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THE ELECTROPHORESIS OF EGG WHITE AND CRYSTALLINE EGG ALBUMIN

SAMUEL GROSBERG, M.D.
and
M. MURRAY PESHKIN, M.D., F.A.C.A.
New York City

ANY method by which allergenic molecules are introduced into the skin without breaking the skin would be of service in a study connected with basic skin physiology. Such a technique might also be of service in placing upon a more quantitative basis the method of skin testing in the allergies. A clue to a method of this type was given when it was shown by Abramson and his co-workers that the active molecules of pollen extracts may be electrophoretically transported into the human skin.[2,3,5] Abramson[4] has further shown that the main route by which these water-soluble molecules were transported was through the sweat glands rather than through the hair follicles. This was a new method of studying skin reactions by allergenic materials provided that the molecules could be transported by the forces engendered by the electric field. The electrophoretic skin test, therefore, is a technique whereby the allergenic material is introduced not into one site but over many sites with a minimum of skin injury. These observations were confirmed by Morse[8] with pollen and by Dutton[7] with pollen and a few other allergens.

In view of the fact that it seemed desirable to study the complex mixture of egg white in detail, and because a child, skin-sensitive by the scratch test and clinically allergic to egg, was available, it was decided to make a quantitative study of the way in which these egg white preparations may be transported electrophoretically into the human skin. In this way data pertinent not only to skin permeability to these molecules which are different from pollen might be obtained, but in addition fundamental observations on the patient's reactivity to egg white molecules introduced into the skin to form skin deposits would be observed.

METHOD

A galvanic circuit with single electrodes, canton flannel pads, and aluminum contacts previously described, was employed.[5] A special electrophoretic apparatus to be described was also tested.[4] A current density of not more than 0.5 ma per cm^2 employing both poles, was used. Because of the extreme clinical and skin sensitivity of the patient, small areas only were tested, the maximum area being 4 cm^2, with the time three minutes. Suitable control experiments were simultaneously made.

A stock solution of egg white was made up without saline. This was done to prevent the salt solution from carrying the current rather than the allergenic molecules themselves, and to preserve electro-osmotic flow within the skin near its maximum. The stock solution of egg white was diluted with glycerin so that in general the dilutions were made from a 50 per cent solution of glycerinated egg white. Since egg white contains approximately 17 per cent protein or protein-like material, the stock solution contained 8 per cent of egg protein. Crystalline egg albumin was chemically prepared in the usual manner.

SUBJECT

The experiments were done on N. R., a white boy, four and one-half years old, first seen on October 7, 1947, when he weighed 35 pounds and was 41 inches tall. At the age of three months a rash appeared on both thighs. The rash spread to other parts of the skin and was aggravated each year during the summer months except for 1947, when the skin cleared from June to mid-September.

At four years of age the oral administration of aspirin caused urticaria. On September 7, 1947, whole milk was accidentally spilled on his chest and soon hives appeared over the areas of the skin in contact with the milk.

Sneezing and leaking from the nose lasting for several hours after arising in the morning commenced at the age of two and one-half years. These perennial nasal symptoms were aggravated during the summer months. At the age of about three years, during the winter, he experienced the first attack of asthma. Subsequent attacks occurred at intervals of one or more weeks with each attack lasting several days. Some of these attacks of asthma were accompanied by a fever and were initiated by infection of the upper part of the respiratory tract. Ingestion of egg also caused asthma.

There were no important childhood diseases. A paternal aunt had eczema.

Physical examination was essentially negative except for a grayish pallor of the mucous membranes of the middle turbinates and dry, elevated, red patches on the skin involving the left wrist, penis, thighs, and the lower abdominal area.

Sensitization skin tests (scratch and intradermal techniques) revealed

positive reactions to egg white, lactalbumin, mustard, pork, radish, white potato, spinach, grass pollen, plantain, and chicken.

Diagnosis: Neurodermatitis (chronic eczema), contact urticaria (milk), drug urticaria (aspirin) and allergic rhinitis (perennial and seasonal).

The boy was placed on a restricted diet, which removed eggs in any form and permitted the use of evaporated cow's milk, along with anti-allergic environmental contact restrictions. External medication was employed for the eczematous skin lesions. After the fourth day, the skin lesions showed progressive improvement until the skin cleared except for one small patch of dry eczema on the dorsal aspect of the left wrist which remained in the following year of 1948, when the electrophoretic experiments with the egg white antigens were begun.

EXPERIMENTS

The experiments were done at intervals of one week. The anterior aspect of the forearms was used in all experiments. The 50 per cent egg white-glycerin mixture (approximately 8 per cent protein) was diluted with water, with a control of a similar dilution with 50 per cent glycerin.

April 27, 1948: With the solution of $1:10^6$ of the egg white mixture and employing the positive pole, no erythema was observed. Few papules appeared on the margin outside of the treated area. These papules were due to the extra pressure of the metal electrode. This test-reaction was recorded as negative.

April 20, 1948: With a $1:10^5$ solution with the positive pole after five minutes, a few papules appeared with slight erythema about them. The papules appeared at the orifices of the sweat glands. A similar reaction was obtained with the negative pole at the end of two minutes, with practically no erythema. The reaction was regarded as faintly slightly positive. The control was negative.

April 13, 1948: A $1:10^4$ solution with the positive pole showed no immediate reaction, but minute scattered discrete papules appeared at the orifices of the sweat glands, the discrete papules fusing so that a confluent wheal was formed. The papules disappeared after thirty minutes. Reaction with the negative pole disappeared within forty-five minutes. The reaction was recorded as slightly positive. The control was negative.

February 10, 1948: With a $1:10^2$ solution and with positive pole, an erythema appeared at once on removal of the electrode, showing a distinct pore pattern within two minutes. There was marked erythema of about 1 cm about the wheal. The size of the wheal corresponded to that of the electrode. With the negative pole the pore pattern was similarly visible after two minutes with a fairly large erythema. The reaction was recorded as moderate. The control was negative.

February 3, 1948: With a 1:10 solution whealing reaction, an erythema was observed with both poles. This was recorded as a marked reaction. The control was negative.

With the crystalline egg albumin solution, commencing with 1:10,[5] positive reactions were obtained only with the negative pole; with 1:10,[4] a large wheal was obtained.

Systemic or Constitutional Reactions.—This patient had two episodes which can readily be interpreted as constitutional reactions following the electrophoresis of the 1:10 and the 1:100 solutions of the 50 per cent egg white-glycerin mixture. About four hours after each electrophoretic test the patient had fever which ranged from 101 to 102 F., with a cough and running nose. The fever lasted one day. The cough and running nose persisted for several days. These experiments were done one week apart.

DISCUSSION

It has been recognized for many years that egg white is a complex mixture of proteins. These are usually classified as ovalbumin, conalbumin, ovamucoid, mucin and globulin. Which of these have been responsible in patients sensitive to egg white has not been explicitly determined on a quantitative basis. On subjecting dilutions of egg white to electrophoretic analysis by the moving boundary method, it was first reported by Young[9] that five or six boundaries could be seen. Indeed, some of these boundaries seem to be complex, indicating that more than six boundaries were present. On the other hand, egg white in the ultracentrifuge showed one sedimenting boundary, indicating that a complex equilibrium existed. In a more thorough investigation of the problem, the nature of these fractions was studied more completely and the isoelectric points of the various components were determined. These varied in a 0.1 N salt solution in one series of experiments, from approximately pH 4.3 to pH 5.9. The widespread range of the isoelectric points in the mixtures may, therefore, account for the fact that both the positive and the negative poles were effective in producing the skin reactions observed here. For example, at pH 5.4 in the complex mixture there are both negatively and positively charged components. The skin in these experiments, as previously shown for ragweed extract solutions, acts as an electrophoretic fractionation membrane. With the positive pole, the negatively charged constituents are prevented from going into the skin, and vice versa. Thus the egg white system, although similar to the ragweed system in having both poles effective, is nevertheless different because of the electrification of the molecules in the system. It would be desirable to fractionate egg white electrophoretically and study the way in which skin reactivity to the various fractions varies with the nature of the fraction.

In this experiment the crystalline egg albumin reacted positively only with the negative pole. This has not been demonstrated heretofore. It indicates that the chemical purification of this preparation, which did not

show the same reaction as the mixture of egg white, provides a new tool for studying skin permeability in the allergic patient as well as certain immunologic reactions.

CONCLUSIONS

In electrophoresis of a mixture of egg white in 50 per cent glycerin on the skin of a child clinically sensitive, faint positive reactions were obtained with a $1:10^5$ solution. With stronger solutions of egg white mixture, the skin reactions were also correspondingly stronger until the maximum reaction was obtained with a 1:10 solution. Both the positive and negative poles were effective in producing the skin reactions.

With the crystalline egg-albumin solutions, positive reactions were obtained only with the negative pole. To avoid unfavorable reactions, only the $1:10^5$ and $1:10^4$ solutions were employed for testing.

On two occasions, systemic or constitutional reactions occurred, commencing four hours after the electrophoresis of the 1:10 and 1:100 solutions of the 50 per cent egg white-glycerin mixture. There was an elevation of temperature and cough and leaking of the nose lasting for one day and several days, respectively.

The purification of egg white may provide a new tool for studying skin permeability in the allergic patient as well as certain immunologic reactions to the fractions obtained.

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450 West End Avenue
(Dr. Peshkin)

INFECTION IN THE ALLERGIC CHILD

BEN F. FEINGOLD, M.D.

Los Angeles, California

BEFORE undertaking a consideration of infection in the allergic child, it is necessary to clarify our understanding of the term "allergy." The great confusion that exists is well expressed by Rich[18] in his text on the *Pathogenesis of Tuberculosis*. "As for the term 'allergy,' that word has become so debauched by indiscriminate usage that it would be fortunate indeed, if it could be dropped completely from the vocabulary of science. It is now applied to such diverse and unrelated types of altered bodily states that it has become a fertile source of confusion and misunderstanding. Some writers use the term 'allergy' to indicate all types of hypersensitiveness to foreign antigens, whether bacterial or non-bacterial; others limit the term to particular types of hypersensitivity; others include drug idiosyncrasy, still others apply the term to all changed reaction capacities that result from contact of the tissues with antigens, including not only all forms of hypersensitivity, but also all forms of acquired immunity, whether antibacterial or antitoxic; others write freely of 'physical allergy,' i.e., hypersensitiveness to heat, cold, or sun light; and Von Pirquet, who created the word finally in his last monograph on the subject ('Allergie des Lebensalters') extended its meaning to embrace even the general bodily changes that occur with advancing age, and which favor the development of malignant tumors. To extend the meaning of the word 'allergy' to include every conceivable sort of bodily change, simply robs the term of all possible usefulness and creates the most unfortunate confusion; and this especially since those who use the term rarely take the trouble to state clearly the particular meaning which the word holds for them."

The term "allergy" has become so deep-rooted in both scientific and everyday usage that to delete it from our language would be an almost impossible task. We are victims of convention, but recognizing this, we apply the term "allergy" to all altered states of tissue resulting from antigen-antibody interaction. The nature of the tissue alteration in great measure depends upon the quality of the antigen evoking the response. Such common allergic syndromes as hay fever, asthma, and eczema are characterized by reversible tissue changes which are activated by non-bacterial antigens which produce increased capillary permeability, edema, smooth muscle

From the George Piness Allergy Group and the Department of Allergy, Los Angeles Children's Hospital.

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stimulation, and increased activity of glands. These responses are in striking contrast to the fixed changes resulting from death of tissues which are the consequences of the action of bacterial antigens upon susceptible tissue. With tissue destruction there is no restitution. On the basis of fixed tissue responses such seemingly diverse clinical entities as rheumatic fever, glomerulonephritis, periarteritis nodosa, lupus erythematosus, dermatomyositis, and post infectious encephalitis are currently attributed to the phenomena of allergy.

There are immunological differences between the two types of tissue responses. In the reversible or non-bacterial type of tissue hypersensitivity the skin test is characterized by an immediate whealing of short duration; antibodies are present in the circulating blood which are demonstrable only by passive transfer or biological tests; and *in vitro* contact of hypersensitive cells with a specific antigen does not produce death of cells. In the non-reversible or bacterial type of tissue hypersensitivity the skin test reaction is delayed like the tuberculin test; antibodies in the circulating blood are demonstrable *in vitro* as precipitins or agglutinins; passive transfer is not possible, and *in vitro* contact of hypersensitive cells with a specific antigen produces death of cells.

Appreciating that the tissue response in a hypersensitive organism is determined by the quality of the antigen, we recognize that non-bacterial substances, such as pollens, epidermal factors, and foods evoke reversible tissue changes and distinct immunological phenomena which explain the symptomatology of such common diseases of the clinic of allergy as hay fever, asthma, and eczema; while bacteria and bacterial products assert themselves in fixed tissue reactions with different immunological responses which are clinically identified with rheumatic fever, glomerulonephritis, and the collagenous diseases. Acknowledging the distinct difference in tissue response to the two types of antigens, we do not accept either bacteria or bacterial products as the etiological agent of such conditions as hay fever, asthma, or eczema whose symptoms result from reversible tissue changes.

What adds to the confusion in recognizing the etiological agent in allergy is the additional factor of the ability of infection to influence the course of existing allergy without any participation on the part of infection in the underlying allergic tissue changes. In other words, infection plays a dual role in tissue hypersensitivity. First, infection may produce fixed tissue changes in the hypersensitive organism and, second, it may influence the course of existing allergy.

When infection does influence the course of existing allergy, it produces a distinct pattern for the allergy. The pattern observed is

one of two types, the type being determined by the nature of the infection. The first pattern (Fig. 1) is observed in association with pertussis, measles, chickenpox, mumps, Kaposi's disease, roseola infantum, and the epidemic viral diseases. With these diseases,

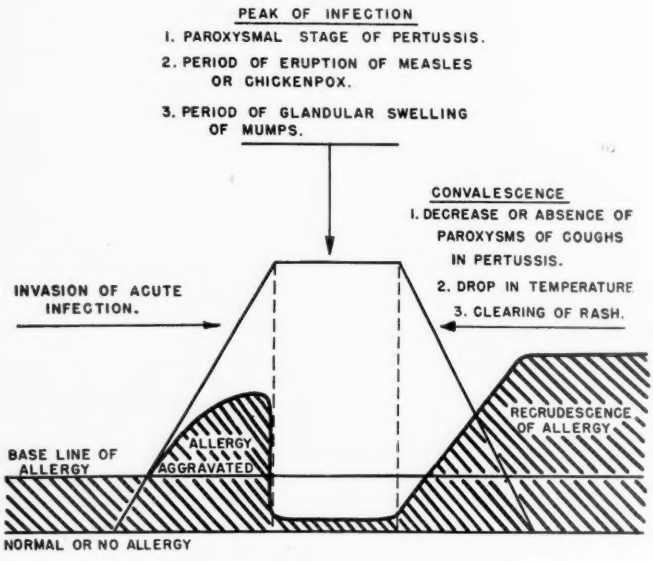

Fig. 1.

during the prodromal stage or period of invasion there is an aggravation of the pre-existing allergy. The symptoms presented during this period will usually be determined by the patient's previous complaint so that the child with allergic rhinitis will have more severe nasal symptoms; the asthmatic child will suffer with asthma or allergic bronchitis; and the eczematous child will present an aggravation of his eczema. As these acute processes approach their full development, the symptoms of allergy become less severe, so that at the fastigium of the disease the child will be free of symptoms of allergy. The nose will be clear; the lungs will be clear; the skin will be clear. Actually, at the peak of these infections the level of allergy is less than prior to the invasion of the acute infectious process. This period corresponds to the paroxysmal stage of pertussis, the exanthem of measles, the eruption of chickenpox, the vesiculation of Kaposi's disease, and the fever of epidemic viral diseases. With convalescence there is recrudescence of the allergy. With convalescence the allergy may recur, and when it does recur it may appear with greater severity and greater intensity than

existed prior to the onset of the acute infectious process. A new base line for the allergy is established, so that the child with mild symptoms of allergic rhinitis may complain constantly of nasal distress; the asthmatic child may have persistent pulmonary findings,

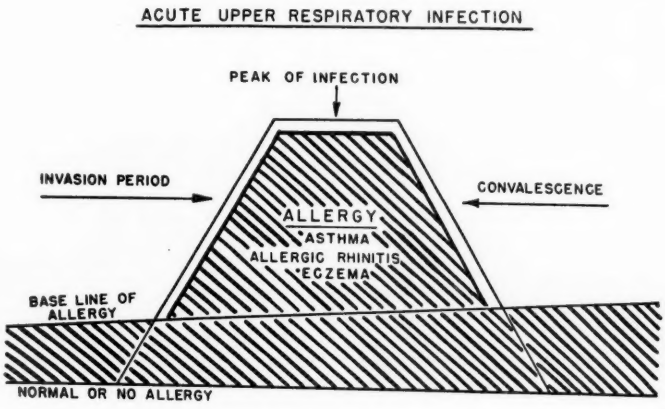

Fig. 2.

or in some instances experience his first attack of asthma; the eczematous child will show an aggravation of his rash.

The second pattern (Fig. 2) is observed most commonly in association with acute infection of the upper respiratory tract, that is, rhino-pharyngitis, acute tonsillitis with or without adenitis, adenoiditis, sinusitis, acute otitis, or any combination of involvement of the upper respiratory tract. With these infections there is no apparent change in the degree of the allergy during the period of invasion, but at the height of the infection there is an aggravation of the allergy. Corresponding to the peak of the infection, the allergy is most severe. The child with allergic rhinitis will have severe nasal symptoms, the asthmatic child will suffer with severe asthma or allergic bronchitis, while the rash of eczema will be aggravated or itching is frequently more intense.

DISCUSSION

An analysis of some of the observations and attitudes on infection in the allergic child expressed in the literature in comparison with the two patterns presented raises some interesting points for discussion.

The exacerbation of allergy by measles is mentioned by Peshkin,[12] who observed that asthma frequently recurred or was aggravated during the incubation period of measles, but with the appearance of fever the asthma cleared in the majority of these patients.

No other such observations has been noted in the literature. The lack of further reports on the exacerbation of allergy during the invasion of an acute infectious process can perhaps be explained by its failure to occur as a constant finding. As the degree of aggravation of the allergy during this phase of the acute infectious process is usually not as severe as that seen following the disease, the clinician may overlook this observation unless he is alert to the over-all pattern produced by an acute infectious process in the allergic child. In some cases, during the invasion of a contagious disease, the symptoms of allergy may return with greater violence and fail to respond to the usual medical management. With the establishment of the fastigium of the disease the symptoms of allergy disappear completely. This observation is not peculiar to children. A woman, aged thirty-seven, whose asthma of many years' standing was controlled with a pollen antigen, had a sudden recurrence which persisted for ten days, when it cleared with equal suddenness. The cough present since the onset of the atshma increased in severity and became paroxysmal. During this stage the chest was clear. The blood count revealed 12,000 leukocytes with 44 per cent polymorphonuclear leukocytes, 54 per cent lymphocytes, and 2 per cent monocytes. The diagnosis was pertussis. Similar history was experienced in a woman, aged twenty-eight years, whose asthma was under control. For one week prior to the establishment of clinical signs of parotitis the patient experienced a severe attack of asthma. Concomitant with the swelling of the parotid glands, the asthma cleared.

Improvement of the signs and symptoms of allergy at the peak of an acute infectious process is also reported in the literature. Very early in the history of clinical allergy, Von Pirquet observed that a positive tuberculin may become negative during measles. In a discussion of desensitization, Rich[18] also points out "that the cutaneous reactivity to tuberculin often diminished markedly during the early stage of the exanthem of measles, to return again after a week or two. A similar diminution in reactivity has been observed during other acute infections." The clearing of eczema with measles is a common clinical observation. We have already noted Peshkin's[12] observations that asthma cleared with the appearance of fever of measles. Very little note has been made in the pediatric literature of the very important observation that a positive tuberculin becomes negative during the paroxysmal stage of pertussis,[1] which was reported by Galli,[9] Pospischill,[14] Hamburger,[10] and Reiche[17] and others, [2,3,11,13] at about the same period that Von Pirquet reported on the tuberculin response during measles. The writer has questioned many clinicians, both pediatricians and allergists, and none can recall the occurrence of asthma during the

paroxysmal stage of pertussis. Rackemann[15] states that when allergy is well established the effect of an intercurrent infection will depend upon its severity. An acute infection of relative severity he states may alleviate the allergy temporarily. The allergic

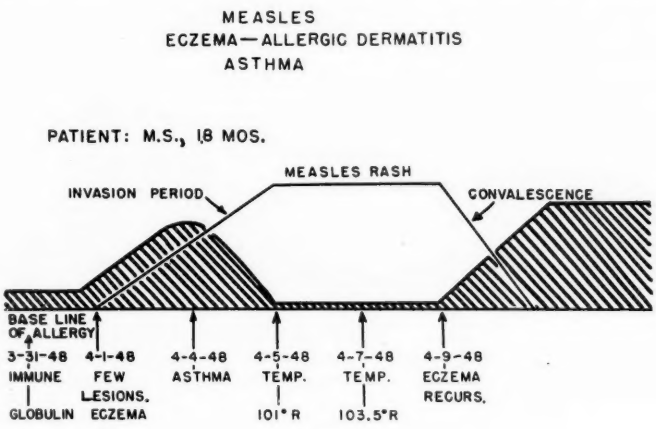

Fig. 3.

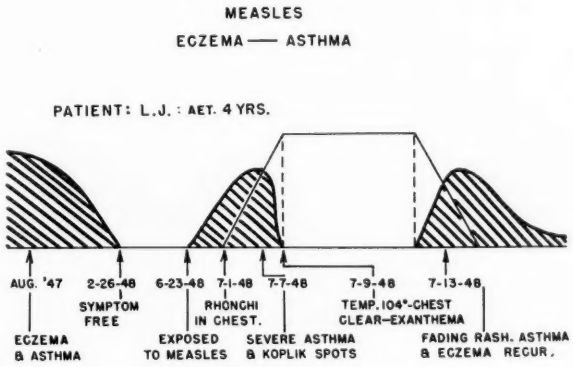

Fig. 3a.

child who gets measles will lose his eczema or asthma at the time of the intercurrent disease. Rackemann's opinion differs from our experience. The influence upon the allergic state is not related to the severity of the infection but to the nature of the infection. The acute infectious diseases, measles, mumps, chickenpox, and pertussis will show an improvement in the allergic state at the peak of the infectious process without relation to the severity of the infection.

In Figure 3, illustrating eczema influenced by measles, the

child suffered a modified measles following the administration of immune globulin. In Figure 3a, illustrating the influence of measles on the course of asthma, the child suffered with a severe reaction to his measles, but during the period of intense eruption

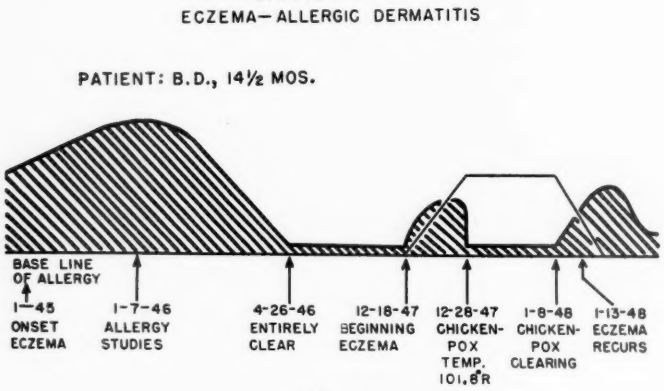

Fig. 4.

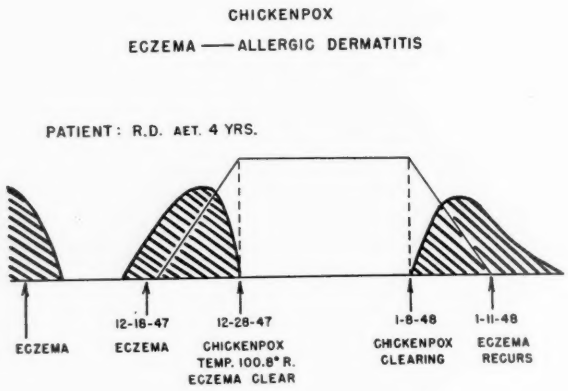

Fig. 4a.

his chest was clear and there were no symptoms of asthma.

In Figures 4 and 4a, illustrating eczema influenced by chickenpox, one child suffered a severe infection with chickenpox while the other child had only a mild infection. These cases serve to illustrate that severity of the infection is not the influencing factor. With the acute infectious processes, regardless of the intensity of the infection, allergy will improve, while in the upper respiratory infections allergy is aggravated at the peak of the infection. Here again, severity of the infection is not the determining factor. This

would seem to indicate that the nature of the infection is the influencing factor rather than degree of infection.

The contention that fever is the determining factor when allergy improves during the course of an acute infectious process can be disclaimed by the same argument. During the course of the diseases mentioned in association with pattern 1, clinical allergy will improve without regard to the degree of fever while in severe upper respiratory infections accompanied by high temperatures, as high as 104° or 105°, the allergy may be aggravated. Fever may be a manifestation of an allergic response, as is observed in serum sickness, the classical example of the acute allergic reaction, or, as has been more recently observed, in penicillin reactions.

There is a difference in the immunological responses in the two groups of infections, as is evidenced by the fact that the first group calls forth a leukopenia or lymphocytosis in the blood picture, while the second group evokes a polymorphonuclear leukocytic response. The first group usually confers an immunity after a single infection while the second group confers no immunity. This immunological difference between the two groups of infections is consistent with the observations reported by Bunting[5] and also Ehrich and Harris.[8] These investigators state: "That the polymorphonuclear leukocyte does not play a part in antitoxic immunity seems to be indicated by a series of clinical observations which have been summarized in a general law of pathology to the effect that no disease which runs its course with a neutrophil leukocytosis is followed by lasting immunity. A high lymphocyte-monocyte ratio suggests resistance."

The aggravation of the allergic state by an infectious process as evidenced by the onset of the first attack of asthma is well recorded in the literature. Practically every modern text on either pediatrics or allergy cites the infectious processes as precursors in the onset of asthma and emphasizes the frequency of pertussis as an exciting agent.

In a study on the incidence and significance of various diseases and infections in asthma in children, Peshkin[12] pointed out the frequency of association of pertussis and measles with the onset of asthma. Walzer[20] states that among the common contagious diseases of childhood involving the respiratory tract, pertussis outstrips all others as an etiologic factor in asthma. Walzer also reports that a number of non-sensitive middle-aged asthmatic patients date the onset of their asthma to the influenza epidemics of the last decade. Bray[4] observes that at least one out of each three cases of asthma will assign the onset to some infectious disease, and whooping cough and pneumonia are by far the most common. Dienes[7] states that no doubt at certain times certain changes occur

which predispose to sensitiveness. During infections such as whooping cough, that part of the system which makes antibodies is much more irritable. He believes that sensitiveness frequently follows infections. Rackemann[15] reported a similar attitude when he states that an acute infection irritates that part of the system which makes antibodies. Asthma may often begin after whooping cough, measles, or other acute infections. In reporting on prophylaxis in allergy, Ratner[16] also emphasizes the importance of measles and pertussis in antedating asthma. In a discussion on the etiology of asthma, Tuft[19] indicates the frequency of a history of pneumonia, influenza, or pertussis prior to the onset of the initial asthmatic attack. In his text *Allergy in Theory and Practice,* Cooke[6] expresses the opinion that "A clinical history of an acute infection especially measles, pneumonia, influenza, or bronchitis as the precursor of an allergy is obtained too frequently to be overlooked or to be rejected as of no moment. Infection as provocateur of an allergy but not specifically and causally related to that allergy is an idea that must be investigated further." Cooke's statement is very pertinent. The infectious processes may not only play a definite role in the causation of clinical allergy, but as illustrated by Pattern 1 may have a distinct influence upon the course of the allergy. The occurrence of clinical allergy following an acute infectious disease is only one phase of the interplay between allergy and the acute infectious processes. The influence of the infectious processes upon the course of allergy raises many problems for investigation. Why is the alteration in the pattern of the allergic state by the infectious processes not a constant manifestation? In some cases the aggravation of the allergic state during the period of invasion may be observed with no recrudescence during or following convalescence. On the other hand, the exacerbation of clinical allergy following an acute infectious process may occur without any apparent influence upon the allergy during the phase of invasion. That this clinical observation is not uncommon is implied by the literature, which frequently mentions the acute infectious processes as precursors of clinical allergy. The only constant observation is the improvement of the allergic state during the fastigium of the infectious diseases. Correlation of these clinical observations with immunological studies would no doubt reveal the answers to some of these clinical phenomena.

The aggravation of the allergic state by the acute respiratory infections is generally accepted in pediatric practice and is cited frequently in the literature by observers reporting on infection in allergy. The allergy is most severe at the peak of acute infection (Fig. 5). The allergic symptoms in association with this type of infection do not respond to the usual medical management for

allergy. The best response is observed following the use of antibiotic drugs, either sulfonamides or penicillin. As the infection subsides, the symptoms of allergy improve without any specific therapy directed toward the allergy.

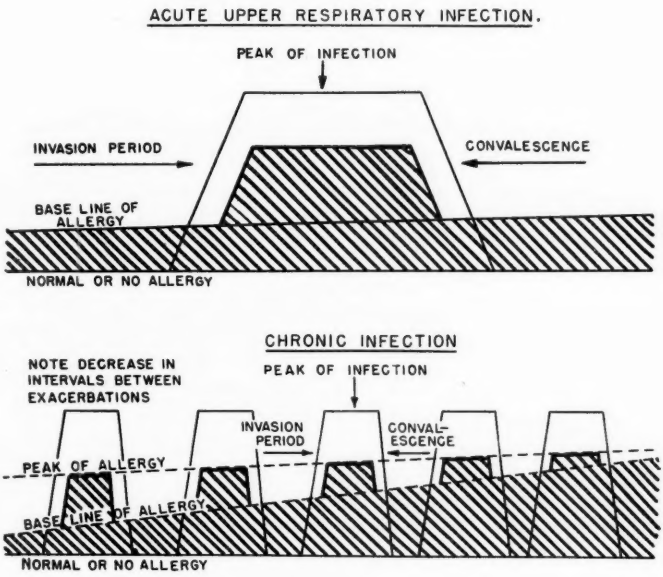

Fig. 5.

In chronic infection of the upper respiratory tract, which includes all chronic infections of the lymphoid tissue of the nasopharynx, the tonsils, adenoids, sinuses or cervical nodes, and in lymph node infection secondary to infected allergic dermatitis, a pattern similar to that just described for allergy in association with acute infections of the upper respiratory tract is observed (Fig. 5). Chronic infection is merely a repetition of the pattern seen in association with acute infection of the upper respiratory tract. During the interval the patient has symptoms of allergy of a varying degree. With each acute flareup of the infection as treatment is directed against the infection, the allergy shows a definite improvement by returning to what is apparently its former level. These children present a great degree of periodicity. They offer a history of acute exacerbation of both the infection and the allergy at regular intervals. This periodic recurrence of the acute symptoms presents a cyclic pattern with a free interval between attacks varying with the individual patient from several weeks to several months. As has been mentioned, during the acute period of the

infection the symptoms of allergy are aggravated but improve as the acuteness of the infection subsides. If one carefully reviews the history of these cases for a period of many months or, in some instances, several years, it will be observed that there is a gradual increase in the level of the residual allergy so that with each succeeding attack of acute infection there is an increase in the severity or intensity of the allergy. Eventually following repeated attacks of acute infection the child's allergy may reach a level which practically incapacitates him. This is the child who comes to the pediatrician or allergist offering a history of a mild allergy at the onset, with frequently recurring infections followed by a gradual increase in the intensity of the allergy. As a result of the severity of the symptoms, that is, of both the infection and the allergy, these children usually present a marked degree of impaired nutrition. They are pale, wan-looking, with deeply circled eyes giving them the expression we refer to as the "allergic facies." They offer the appearance of being markedly anemic, but a blood picture usually shows the absence of any anemia.

Early in the development of this particular pattern, the acute exacerbation of infection responds extremely well to specific therapy with the antibiotics. With recovery from the acute infection, the co-existing allergy improves. It is this particular response of the allergy, following the use of antibiotic drugs which are directed against the infectious process, that leads many pediatricians and, for that matter, many allergists, to consider bacterial sensitivity as the underlying cause of the signs and symptoms in this group of children. But such reasoning does not take into consideration the fixed tissue changes which characterize the pathology of hypersensitive tissue in response to infection, nor the clinical observation that the signs and symptoms of allergy are present during the interval between acute exacerbation of the infection. The allergy may be less severe but it is constantly present. The nasal mucosa is still edematous, the turbinates are still swollen, there is still considerable discharge from the nose with post nasal drip producing cough. The lungs during the interval may reveal rhonchi and some wheezing. All these findings may be present during the interval between attacks, but during the acute phase of the infection they become aggravated because of the influence of infection upon existing allergy.

Further clinical evidence for such reasoning is the observation that a child who offers a history of allergy with recurrent upper respiratory infections will show a definite control of his allergy when under competent allergy management. In other words, a child may have an upper respiratory infection but it is not accompanied by the symptoms of allergy when his allergy is con-

trolled. That a relationship exists between infection and allergy is evidenced from the patterns observed. The infectious diseases have a definite influence upon the clinical picture of allergy in childhood; yet one would not accept either pertussis, chickenpox, measles, or mumps as part of the etiology of allergy. Similarly, because upper respiratory infections influence the existing allergy, they should not be considered the etiologic factor of the allergy. The co-existence of allergy and infection does not necessarily mean bacterial sensitization. That the relationship between infection and allergy acts in both directions is evidenced first by the absence of the allergic symptoms in the presence of upper respiratory infection when the allergy is under control through treatment, and second, by the decrease in the severity and incidence of upper respiratory infections when the allergy is under control.

As has been indicated, following each exacerbation of a chronic infection the allergy may return to a somewhat higher level than existed prior to the onset of the acute symptoms of infection. Eventually, after repeated acute attacks of the infection, a level is reached at which the influence of the infection upon the allergy is so great and the base line for the allergy is so high, that even specific therapy directed against the infection influences the allergy very little, if at all. What is further interesting, in this particular state specific therapy directed against the allergy often has little influence on the allergy. It will be observed that these children frequently present a marked degree of sensitivity and their tolerance for even very weak dilutions of antigen may be extremely poor. Successful management in this type of patient is contingent upon (1) eradicating the foci of infection, and (2) instituting competent management for the allergy.

The most frequent focus of chronic infection in the child is in the upper respiratory tract. In this group of children, it is a common error for the clinician to direct his attention toward clearing the infection without specific management for the allergy. This practice occurs quite frequently because following the removal of the foci of infection the condition of the child may improve so markedly that he is not only free from complaints of infection but the symptoms of allergy also clear up. He may be free from symptoms of allergy for a considerable period of time. It is quite important, however, that this group of children, especially those who have had a tonsillectomy or adenoidectomy, should receive immediate, intensive, and intelligent management for their allergy. It is only through such management that one can hope to prevent the recurrence of the factor of chronic infection which complicates the allergy. If the child fails to receive adequate management for his allergy, there is a greater likelihood that the

lymphoid structures of the upper respiratory tract will show hyperplasia with ultimate chronic infection followed by a return of the picture which has just been described for allergy with chronic infection. Once infection sets in again the pattern is repeated, and when the pattern is repeated the management is extremely difficult because controlling the infection in the lymphoid structures which have regrown presents problems which tax the ingenuity of the rhinolaryngologist, the pediatrician, and the allergist.

The recognition of the patterns that occur with infection in the allergic child suggests many clinical applications:

1. The aggravation of the signs and symptoms of allergy after exposure to an acute infectious disease should suggest the prodromal stage of the acute infectious process.
2. The sudden abatement of the allergic symptoms immediately precedes the eruptive stage of measles and chickenpox or the parotitis of mumps. With a history of exposure to either chickenpox or mumps this observation should be particularly valuable in the diagnosis of these diseases where no diagnostic findings precede either the rash or parotitis.
3. The sudden improvement in acute asthma or allergic bronchitis with a persistence or aggravation of the cough should suggest pertussis as a likely complication.
4. In measles, the asthma or allergic bronchitis will clear just before the exanthem appears. The cough persists and is very harassing. At this stage the exanthem may not be typical. The clearing of the allergy and a persistence of cough should suggest the period immediately before the exanthem when measles is suspected.
5. Following an acute infectious disease, an aggravation of the allergy can usually be anticipated. This may occur during clinical convalescence or a few days to several weeks following clinical convalescence. Perhaps in some cases clinical and immunological convalescence do not parallel.
6. If the allergic state is aggravated following pertussis and the acute infectious diseases, then it should be exceedingly important to protect the allergic child against such diseases. For pertussis it means adequate immunization, and for measles, protection with immune globulin.
7. The cyclic character of the acute exacerbation of chronic infection in the allergic child has been indicated. This should be differentiated from the cyclic picture encountered in the recurrent acute allergic state without infection. In the allergic state, uncomplicated by infection, periodicity may occur with or without fever. In the absence of fever, the patient presents the usual signs and

symptoms for his allergy. In the presence of fever in the allergic state without infection, a cyclic pattern of two types may be observed.

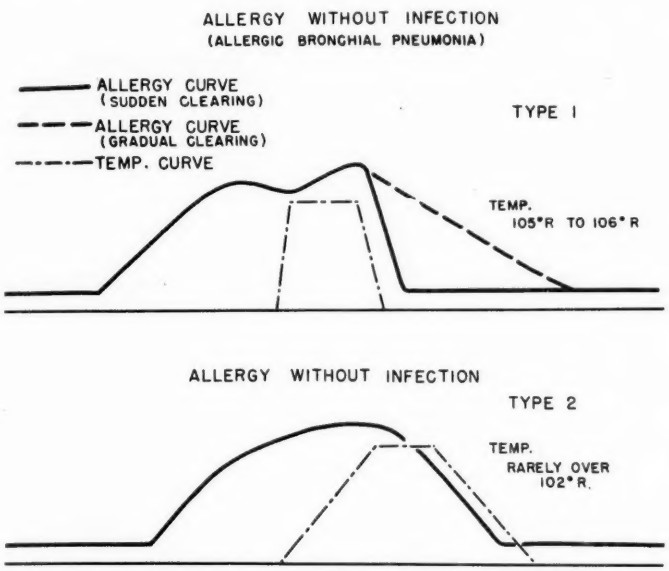

Fig. 6.

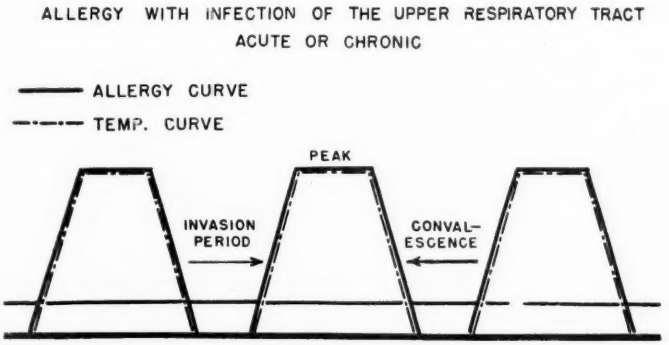

Fig. 7.

(a) The first syndrome is ushered in by the usual upper respiratory tract symptoms of sneezing, rhinorrhea, and stuffiness of the nose followed by cough and the signs and symptoms of asthma or allergic bronchitis. When sudden high fever—105° to 106°—occurs during the course of the asthma or the allergic

bronchitis, it usually means the complication of allergic bronchopneumonia. The recognition of this pattern is important in the management of the patient, as a dramatic response may be observed following the early administration of adrenalin and fluids.

(b) The second picture presents the signs and symptoms of acute asthma or allergic bronchitis, which disappears with the sudden onset of fever. Fever in these cases is rarely over 102° orally as compared to the very high fever of 105° or 106° observed in allergic bronchopneumonia.

Fever ushers in the acute state, in the syndrome of upper respiratory infection plus allergy. The occurrence of fever at the onset of the acute picture should serve as a diagnostic guide in the differentiation from allergy without infection. In the latter, fever occurs after the signs and symptoms of acute allergy are fully developed. This observation can also serve as a guide in the management of these children. In the presence of infection the best response is observed with antibiotic medication. In the absence of infection the usual management for allergy is recommended.

SUMMARY AND CONCLUSIONS

1. Infection plays a dual role in allergy. First, it may participate in tissue hypersensitivity of the fixed tissue variety; and second, it may influence the course of existing allergy.

2. When infection influences the course of existing allergy, it produces one of two patterns depending upon the nature of the infection.

3. With the infectious diseases—pertussis, measles, mumps, chickenpox, roseola infantum, Kaposi's disease, and the epidemic viral infections— allergy is always improved at the peak of the infection.

4. Upper respiratory tract infections aggravate allergy at the peak of the infection.

5. Chronic infection is a repetition of the second pattern presented.

6. Management of allergy with chronic infection usually necessitates clearing the foci of infection and competent treatment for the allergy.

7. Some clinical applications of the patterns presented have been indicated.

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672 So. Westlake Avenue

BRAZILIAN SOCIETY OF ALLERGY

The program of a symposium and plenary session of the Brazilian Society of Allergy, which was held at the Polyclinic, Rio de Janeiro, November 6-11, 1950, arrived as this issue went to press. The following are the officers of the Society: Nelson Passarelli, President; E. Brum Negreiros, Vice President; Haroldo Cardoso de Castro and Newton Guimaraes, Secretaries; Sayao Lobato, Treasurer; and Mario Miranda, Librarian.

The first symposium, on urticaria, was presided over by Prof. Dr. Ramos e Silva. The symposium on eczema was conducted by Prof. Dr. Francisco Eduardo Rabello, on asthma by Prof. Dr. Luiz Capriglioni, and on neuropathic allergies by Prof. Dr. Deolindo Couto. The last two days of the convention were taken up with the plenary session.

THE INTRAMUCOSAL TEST AND A COMPARISON OF ITS REACTIVITY WITH THE INTRADERMAL AND CONJUNCTIVAL REACTIONS

HYMAN SHERMAN, M.D., F.A.C.A., and LOUIS A. FELDMAN, M.D.
Brooklyn, New York

THE purpose of this investigation was to study the nature of the intramucosal reaction and to compare quantitatively the intramucosal test with the ophthalmic (drop) and intracutaneous tests. The ocular conjunctiva, which is readily accessible, lends itself easily for such studies.

Dean, Linton and Linton[2] in 1935 were the first to describe the intramucosal test and the mucosal scratch test. Their work was limited to the nasal mucosa only, and was done in relation to studies in ionization of the nasal mucosa. They found the mucosa to react positively in many cases where the skin tests were negative in patients suffering from allergic rhinitis.

Stevens,[8] Rudolph and Cohen,[1] Efron and Penfound,[3] Peshkin,[5] and others also used various methods of mucosal investigation, utilizing pulmonary inhalations, cotton pledgets in the nose, sprays, powder blowers, and dry pollen in the nose.

Fineman[4] in 1926 made comparisons of the intradermal, scratch, and conjunctival tests.

Ten patients with hay fever were studied. They consisted of two tree, two timothy, and six ragweed pollen cases. No cases which demonstrated any degree of congestion or dilatation of the ocular or tarsal conjunctiva were accepted for study. All skin titration and ophthalmic tests were performed outside the pollen seasons. Five patients had received or were receiving pollen extract treatment; the other five patients had never received treatment.

TECHNIQUE

The tests were performed in the ocular conjunctiva just below the cornea. (Fig. 1). At first a 1 per cent pontocaine solution was used as a topical anesthetic. This did not cause dilatation of blood vessels of any importance nor did it interfere with the results obtained. Most of the cases received no topical anesthesia.

Using a 26-gauge needle, ⅜ inch long, and the standard testing syringe, a tiny bleb containing 1/50 cc of testing material was raised in the ocular conjunctiva of one eye. The other eye was utilized for making comparative tests with the drop method.

Presented at the Fifth Annual Meeting of The American College of Allergists, April 14-17, 1949, Chicago, Illinois.

From the Department of Allergy and the Department of Ophthalmology, Jewish Hospital of Brooklyn, N. Y.

DESCRIPTION OF THE INTRAMUCOSAL REACTION

The reaction developed rapidly. There was an immediate injection and dilatation of the conjunctival and scleral vessels about the test site. The injected vessels had a definite violaceous color. The injection and dilatation

Fig. 1. Appearance of eye prior to intramucosal test.

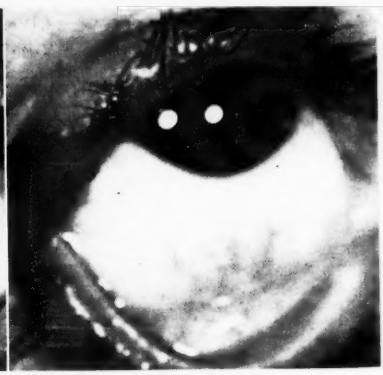


Fig. 2. Control reaction after ten minutes, fading fast.

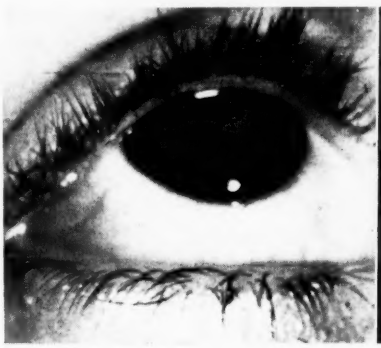


Fig. 3. Reaction after seventeen minutes, showing edema.

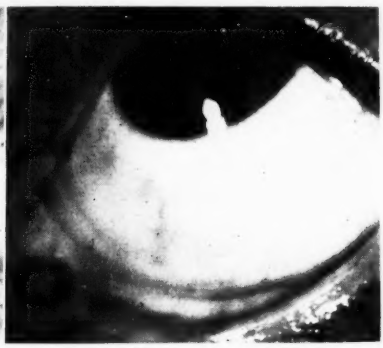


Fig. 4. After drop of epinephrine.

of the vessels increased rapidly, spreading nasally, temporally, and downward involving the caruncle and lower lid. (Fig. 3). Edema and itching were present to only a slight extent. Occasional associated symptoms were slight burning, a sensation of fulness in the eye, and slight tearing of the tested eye. There was usually a clear area between the ciliary ring of vessels, which almost always developed, and the area of dilated vessels below or at the test site. The reaction attained its height in six to ten minutes, and began to fade after twenty to thirty minutes. In the stronger reactions there was a wider and more intense injection and dilatation of the blood vessels and increased edema, which extended down to the lower

lid, and in severe reactions down to the malar eminence (Fig. 3). In the mild reactions the local effect of one drop of epinephrine (1:1000) was rapidly effective on the dilated and injected vessels and the edema (Fig. 4). Epinephrine did not shrink the stronger reactions completely, which as a rule needed a second drop.

CONTROL STUDIES

It was desirable to determine the reactivity of the bulbar conjunctiva after testing with a saline control in an allergic subject. Upon the introduction of 0.02 cc of a buffered saline solution there was an immediate injection of the finer and smaller vessels of the bulbar conjunctiva, which reached its height in about five minutes. There was no involvement of the larger blood vessels, as occurred in the specific type of reaction. The violaceous appearance of the specific reaction was present, but to a lesser degree. The intensity of the reaction was far less than that produced by pollen. The reaction seldom exceeded ½+, reached its height in five minutes, and usually faded in ten minutes (Fig. 2). There was no itching or edema. The shrinking effect of epinephrine upon the control was more pronounced than in the specific reaction. The results were identical in five control subjects studied. Control studies were also done in nonsensitive cases, using timothy and ragweed extracts instead of saline. The reactions were of a similar character, and in no instance did the pollen control in the same individual exceed that of the saline control or vice versa.

COMPARATIVE STUDIES OF OPHTHALMIC AND INTRACUTANEOUS REACTIONS

Threshold intramucosal reactions were compared with simultaneous threshold intracutaneous reactions where possible in each patient studied. In the five patients threshold conjunctival reactions were also obtained in the other eye, using the drop technique at the same sitting. In the other five patients the conjunctival tests were obtained one to two months prior or at a later date.

The results of these comparative studies are shown in Tables I, II, III and IV. In each of the ten cases studied, the intramucosal response was greater than the corresponding intracutaneous test. In six of the cases the difference in reactivity was pronounced. Comparisons of intramucosal threshold reactions were also made in each case with the ordinary conjunctival test, using the drop method. The comparative results demonstrate that the intramucosal test is ten to one hundred times more sensitive than the corresponding intracutaneous test. A comparison of intracutaneous thresholds and conjunctival (drop) thresholds indicates that the intracutaneous test is from ten to one hundred times more sensitive than the ordinary conjunctival (drop) test (Table V). These latter findings confirm the original work of Fineman,[4] and of the author[6] in the comparative reactivity of the skin and of the conjunctiva.

TABLE I. A COMPARATIVE STUDY OF THRESHOLD REACTIONS

Case No.	Type of Case	Rec'd Treatment	Titrations	D F	00001	0001	mg 0005	N 001	per 005	cc .01	.1	Result
1	R A G	no	Intramucosal Intradermal Eye (drop)	1		12 4		8 0	12	1		√ X
2	T I M	yes	Intramucosal Intradermal Eye (drop)			8 1		6	10	1		√ X

Values—1 + Reaction = 4
2 + Reaction = 8
3 + Reaction = 12
4 + Reaction = 16
√ = Greatest response.
X = Least response.

TABLE II. A COMPARATIVE STUDY OF THRESHOLD REACTIONS

Case No.	Type of Case	Rec'd Treatment	Titrations	D F	00001	0001	mg 0005	N 001	per 005	cc .01	.1	Result
3	T R EE	yes	Intramucosal Intradermal Eye (drop)							8 0 0	4 1	√ X
4	R A G	no	Intramucosal Intradermal Eye (drop)	1	8 4	6 0		8 0	10	12 3		√ X

Values—1 + Reaction = 4
2 + Reaction = 8
3 + Reaction = 12
4 + Reaction = 16
√ = Greatest response.
X = Least response.

TABLE III. A COMPARATIVE STUDY OF THRESHOLD REACTIONS

Case No.	Type of Case	Rec'd Treatment	Titrations	DF	00001	0001	mg 0005	N 001	per 005	cc 01	.1	Result
5	R A G	yes	Intramucosal Intradermal Eye (drop)	1		2 3	8	7 0	12	2		√ X
6	R A G	no	Intramucosal Intradermal Eye (drop)	1 4		6 4		8 0		2		√ X
7	T I M	yes	Intramucosal Intradermal Eye (drop)	2 1		8 4		6 0	10	16 2		√ X

Values—1 + Reaction = 4
2 + Reaction = 8
3 + Reaction = 12
4 + Reaction = 16

DISCUSSION—SLIT-LAMP STUDIES

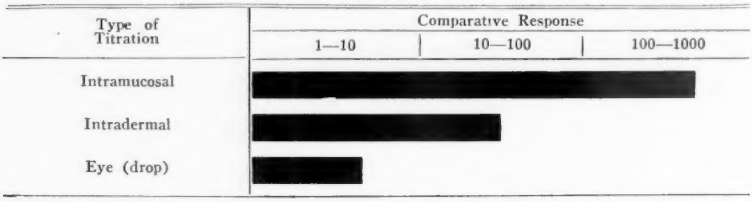
Some of the specific reactions and control reactions were observed under the slit lamp. The findings corroborated those found on gross inspection using the magnifying 100p.

The intramucosal reaction developed instantaneously and reached its height sooner than did the intradermal or conjunctival test, using the drop method. It is a more diffuse type of reaction than that obtained with the drop technique, which is more localized. However, the subjective

TABLE IV. A COMPARATIVE STUDY OF THRESHOLD REACTIONS

Case No.	Type of Case	Rec'd Treatment	Titrations	D F	00001	0001	mg 0005	N 001	per 005	cc .01	.1	Result
8	R A G	no	Intramucosal Intradermal Eye (drop)	3 1	9 3	6		12 0				✓ X
9	R A G	no	Intramucosal Intradermal Eye (drop)		5 3	9 5 0		7 0		1		✓ X
10	T R EE	yes	Intramucosal Intradermal Eye (drop)							12 7 2	14	✓ X

TABLE V. COMPARATIVE REACTIVITY OF TESTS



symptom of itching appears to be more characteristic of the conjunctival pollen test, even in threshold reactions. It was invariably absent in the average intramucosal reaction.

In the specific intramucosal reaction there was a suggestion of corneal dullness resembling edema which could not be seen on gross inspection.

The larger conjunctival vessels were invariably dilated and engorged in the specific intramucosal reaction. In the control studies, using both saline and pollen solutions, the larger conjunctival vessels were not involved in the reaction.

The topical effect of epinephrine was likewise observed under the slit lamp. There was a rapid shrinking of the fine and large vessels, with a consequent diminution of the edema and blush. the epinephrine effect in the specific reaction was much slower than in the control reaction or in the specific conjunctival reaction using the drop method. Edema appeared to persist longer in the specific intramucosal reaction. The shrinking effect of epinephrine on the cornea could be seen in all cases observed.

Fundus studies were negative in all types of reactions. There was no change in lens refraction even in the stronger intramucosal reactions.

Conjunctival titrations are subject to many more technical limitations than are the cutaneous titrations. One great handicap in utilizing the conjunctiva for study is that only two eyes are available in each patient for titration; and good technique does not permit retests of these surfaces at frequent or short intervals. The authors[7] have previously shown that such a technique is subject to considerable error, especially when used for the purpose of quantitative comparison of eye reactions.

The findings resulting from a comparison of the intradermal and eye (drop) tests re-affirm the conception that the conjunctival test is not a sensitive one and, at best, is a crude index of ophthalmic sensitivity.

SUMMARY AND CONCLUSIONS

Ten patients with various types of hay fever were studied. Intramucosal tests were performed in the ocular or bulbar conjunctiva just below the cornea. The reaction developed very rapidly, attained its height in about ten minutes, and began to fade in twenty to thirty minutes. The reaction consisted of dilatation and engorgement of the fine and larger vessels of the underlying conjunctiva and sclera. In the stronger reactions conjunctival edema and injection of the caruncle developed. The cornea did not appear to participate in the reaction. Slit-lamp studies confirmed these findings. It is noteworthy that itching and lacrimation were absent in these reactions.

A comparison of similar threshold reactions revealed that the intramucosal response is at least ten times greater than the intracutaneous reaction, and at least one hundred times more sensitive than the conjunctival test using the drop method.

Suitable control studies were made.

Practical use of the intramucosal test might be made in clinical allergies where skin tests are negative. However the test is not recommended as a routine diagnostic procedure.

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455 Ocean Avenue

FURTHER EXPERIENCE WITH HISTAMINE IN FOREIGN PROTEIN TYPE REACTIONS

HOMER E. PRINCE, M.D., F.A.C.A., and RICHARD L. ETTER, M.D.
Houston, Texas

SINCE our original report[1] we have continued to use histamine in the treatment of severe foreign protein type reactions and have employed this method of therapy in sixty additional patients. Our experience in treatment of this added number of patients has substantiated our previous impressions concerning the value of histamine for these conditions. Huff[3] has reported similar results in the treatment of four patients by this method. In addition we have gained further impressions regarding method of administration of the drug, as well as of the clinical behavior of foreign protein type reactions, especially those caused by penicillin.

By far the greatest offender in this series of foreign protein reactions was penicillin. We have not tried to determine the different penicillin preparations, since adequate history or reliable record could not often be obtained. The following table will show the incidence of the offenders:

TABLE I

Penicillin	44
Tetanus antitoxin	5
Estrogens in oil	2
Vitamin B preparations	2
Demerol	2
Immune globulin	1
Poison ivy antigen	1
Chloromycetin	1
Intramuscular liver preparations	1
Undetermined: (liver or penicillin)	1

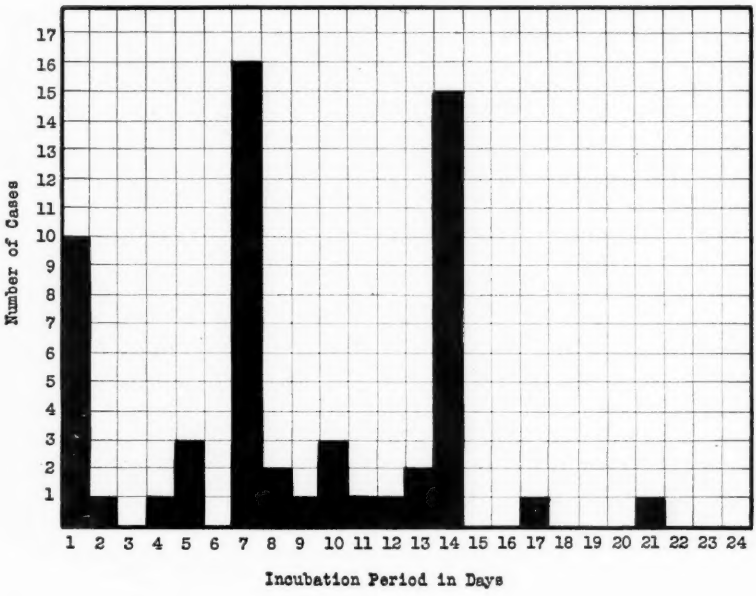
It is of interest to note that the incubation period of the reactions occurred in three distinct groups (see chart). About one fourth appeared as immediate reactions or within about twenty-four hours, another fourth on about the seventh day, and another fourth on the fourteenth post-injection day, while the others were about equally distributed from the second to the twenty-first day.

This pattern of incubation periods very definitely emphasizes a cyclic behavior in the factors determining the foreign protein type reaction. That such a cycle is actually operative is further suggested by occasional relapses in individual patients, or in the persistence of dermatographism or urticaria as a sequel to the reaction; we have observed such relapses or other residual symptoms in some instances to follow a recurring pattern usually of diminishing intensity at periodic intervals.

All patients selected for treatment with histamine had previously been found non-responsive to antihistaminic drugs. Many presented symptoms of great severity including urticaria, angioneurotic edema of variable distribution, itching, temperature elevation, nausea and vomiting, joint pains

Presented at the Sixth Annual Meeting of The American College of Allergists, January 15-18, 1950, St. Louis, Missouri.

INCUBATION PERIOD OF REACTIONS



and swelling, oliguria, exfoliative dermatitis, abdominal cramps, pulmonary edema, hemorrhagic lesions, "ids," psychosis, injection of sclera, yellow discoloration of the digits, headaches, diarrhea, and fainting. In some instances major symptoms had persisted for a considerable period of time before histamine treatment was initiated.

METHOD OF ADMINISTRATION

Intravenous administration of histamine is the method of choice, in that the dosage can be controlled and undue effects can be terminated upon discontinuation of injection. A dose of 2.75 mg histamine acid phosphate in 250 cc isotonic saline or 5 per cent glucose in water is given for the first infusion to determine the sensitivity of the patient. The rate of the infusion is regulated to just produce a generalized flush; too rapid administration may cause severe headache and substernal pain, while a rate insufficient to bring about flushing of the entire skin is usually ineffective.

At first, we followed the procedure advocated by Horton,[1] giving the infusions twice daily, but we soon discovered that improvement was not uniformly sustained in the interval between infusions. We believe that the average patient does better with injections every four to six hours, in the beginning of treatment. In a few cases of extreme severity, continuous administration has been found necessary. When signs have disappeared,

or are minimal, the infusions may be reduced to every twelve hours and eventually to every twenty-four hours.

When rapid administration of the above dosage does not produce a generalized flush of the skin, the concentration of histamine acid phosphate may be increased to 1½, 2, 3, or even 4 ampoules, each containing 2.75 mg in 250 cc of diluent. In five cases we have used 6 ampoules and in two instances as much as 9 ampoules in 250 cc of vehicle.

Late in the series of patients comprising our former report the use of intradermal injections of histamine was instituted. We now feel that intradermal injections are sufficient in a great many cases, or may even be the only method available when veins cannot be entered, or in children, as mentioned in our earlier report. Furthermore, while we admit that intradermal injections do not allow control of the response as rapidly as can be accomplished when histamine is given by the intravenous route, we have encountered no instances of undue side effects which we could attribute to intradermal administration.

Titration of a new patient suffering from foreign protein type reaction, to determine his flushing dosage with histamine administered intradermally, affords at once a valuable prognostic clue regarding how difficult he will be to relieve. If a generalized flush can be produced, further injections of the flushing dose are continued intradermally at intervals of four to six hours, in keeping with the clinical response. On the other hand, if the maximum intradermal dose does not produce good flushing, we know that we must proceed at once to intravenous medication, often with a larger dose than 2.75 mg of histamine acid phosphate in 250 cc of diluent. In general, patients who give adequate flushing with smaller doses of histamine seem to improve more rapidly than those requiring the larger amounts.

The titration is made with increasing amounts of histamine beginning with 0.05 cc of the acid phosphate salt, 2.75 mg per cc, or of the dihydrochloride, 1:1,000; if this causes no flushing after about fifteen minutes, 0.10 cc may be tried. If still no flushing is obtained, the 1:100 concentration of histamine dihydrochloride is employed in doses of 0.02, 0.05, and finally 0.10 cc, or occasionally of intermediate amounts when it seems that adequate flushing is imminent and will require only a slight increase in dose.

RESULTS

Many of our patients have been relieved satisfactorily with intradermal injections once or twice daily, so that the treatment could be carried out entirely in the office. Others have required more frequent injections, and these have either been treated at home or have been hospitalized. Quite often, however, particularly in the severe cases, intradermal histamine did not produce sufficient flush to be effective. All such patients have responded to intravenous medication except one who could not be

flushed with 49.5 mg of histamine acid phosphate (18 ampoules) in 500 cc of isotonic saline administered at a rapid rate.

With properly selected flushing dosage of histamine, whether administered intradermally or intravenously, the acute symptoms of foreign-protein-type reactions in fifty-nine of our sixty patients were satisfactorily controlled. The average duration of treatment was about four days. In most instances all but those patients with extremely severe symptoms manifested definite improvement within twenty-four hours, often after the second or third flushing injection. Many of the patients with severe involvement, on the other hand, especially those with extensive angioneurotic edema and joint involvement, required three or four days before improvement was evident, and in some instances additional time was needed for control of the acute symptoms.

Regardless of the severity of symptoms it occasionally happened that the established dose of histamine ultimately caused increased flushing so that the amount had to be reduced. Such decrease in histamine tolerance seemed to occur earlier in instances of smaller dosage requirements than in the relatively more refractory cases, usually associated with more severe symptoms, which responded only to the larger amounts of histamine. This lowering of histamine tolerance impressed us as being a favorable sign indicating clinical improvement.

Occasionally, various antihistaminic drugs and sedatives, such as codeine or demerol, have been employed along with histamine therapy. We have observed no diminution of the flushing response from histamine due to antihistaminic drugs.

We were impressed with one feature of foreign protein type reactions, particularly those due to penicillin: a fair number of these patients, after recovering from acute symptoms of the disease, developed a state of chronic urticaria or dermatographism, usually of low-grade proportions. While further injections of histamine do not seem to help such strictly urticarial complication, the routine allergy management, such as dietary manipulations, eradication of intestinal parasites, and similar measures, has seemed helpful in several of our cases. On the other hand, many of the cases of dermatographism have seemed to respond to continued treatment with histamine, but in a few instances the dermatographism has not been successfully terminated. We do not know whether the urticaria and dermatographism are due primarily to the foreign protein type reaction or whether the reaction has lowered the threshold to the point that previous subclinical factors have become operative.

DISCUSSION

For the mechanism by which histamine affords relief in foreign protein type reactions we offer no theory beyond what might be expected in view of the known physiological action of the drug. It would seem that as capillary dilatation is effected in the skin and subcutaneous tissues or

in other involved organs or sites, such as joints and periarticular structures, there is set up a process whereby edema lymph and minute traces of antigen deposited in tissue spaces may be returned to the circulatory system for eventual excretion. We have repeatedly observed greatly increased diuresis follow immediately the flushing response to histamine. We have felt that this diuresis, which usually accompanies clinical improvement as manifested by a reduction in local or more generalized tissue swelling, is due more to the mobilization of the fluid element from the swollen areas than to a diuretic action of histamine. On the other hand, it is difficult to say that under certain circumstances histamine does not have diuretic action. The not too infrequent symptom of oliguria associated with severe foreign protein type reactions may indicate that a part of the general reaction has occurred in the kidney parenchyma. Diuresis following adequate flushing with histamine in such an instance would naturally appear to be the result of mobilization of edema fluid from the kidney parenchyma. Horton[2] has observed the diuretic action of histamine in cases of urinary suppression.

SUMMARY

Sixty additional patients with severe foreign protein type reactions, all of whom had been treated previously with antihistaminic drugs, have been treated with intravenous or intradermal histamine. In all but one case there was clinical improvement. Each patient was considered individually in determining dosage and interval between injections.

Persistent dermatographism or urticaria, usually of low-grade proportions, occasionally follows severe foreign protein type reactions, especially those due to penicillin.

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Medical Arts Building
Houston 2, Texas

Irwin P. Lubowe, M.D., announces the removal of his office to 1 West 85th Street, New York 24, N. Y. Doctor Lubowe is an Associate Fellow of The American College of Allergists, and his practice is limited to dermatology and dermatological allergy.

NETHAPRIN IN THE TREATMENT OF RESPIRATORY ALLERGY

FRENCH K. HANSEL, M.D., F.A.C.A.
St. Louis, Missouri

EARLIER reports have described the beneficial effects of a mixture of Nethamine and Butaphyllamine, with and without phenobarbital, in the treatment of nasal and respiratory allergies.[4,5] This compound is supplied under the name "Nethaphyl." Recently, a companion product has been made available under the name "Nethaprin," containing 25 mg of Nethamine (methylethylamino-phenyl propanol) Hydrochloride, 60 mg of Butaphyllamine (theophylline aminoisobutanol), and 6 mg of Decapryn (doxylamine) Succinate in each capsule or in each 5 cc (teaspoonful) of the syrup. Nethamine is a sympathomimetic amine with an ephedrine-like action. It differs from other compounds of this group in having little or no pressor action, seldom producing any significant degree of the usual ephedrine side actions, such as nervousness, palpitation or increased blood pressure.[1] Butaphyllamine has the basic action of other theophylline derivatives with the possible advantages of better absorption and toleration.[8] Decapryn Succinate is an antihistaminic and antiallergic drug with a high milligram potency.[2] Experimentally, it relaxes bronchioles that have been constricted by histamine.[3] The small doses commonly employed at the present time are virtually free from significant side effects.

In the management of respiratory allergy, especially bronchial asthma, drug therapy is employed primarily for the purpose of giving the patient symptomatic or palliative relief. It is, therefore a valuable and indispensable adjunct which must be continued until the patient is free from symptoms.

Our observations on the administration of Nethaprin are based upon two years' experience with 441 bronchial asthma patients. They were given a total of 80,000 capsules and 180 ounces of the syrup, usually in dosage of one or two capsules (or teaspoonfuls) three times daily. The writer followed more than half of these patients personally during the administration of a total of 56,000 capsules and all the syrup. For the remainder of the clinical material he is indebted to collaborating members of the Hansel Foundation who kindly contributed case histories for the study.

As might be expected, the degree of satisfactory response to Nethaprin in bronchial asthma parallels the degree of severity and chronicity of the disease. The response was satisfactory in a large percentage of the chronic cases. Actual degree of relief depended upon the extent of the patient's symptoms as contributed by such complications as emphysema and chronic bronchitis. The milder cases, particularly of the paroxysmal type,

"Nethaphyl," "Nethaprin," "Nethamine," "Butaphyllamine," and "Decapryn" are trademarks of The Wm. S. Merrell Company, Cincinnati, Ohio, from whom clinical supplies for this study were obtained.

responded very satisfactorily. In such cases the relief from each attack was highly gratifying in from 85 to 90 per cent of the cases.

On the whole, the response of therapy with Nethaprin in older children, age eight to twelve years, was most satisfactory. Usually, a single capsule or one teaspoonful of syrup given three times daily was adequate in these cases.

Nethaprin appears to have a synergistic action which tends to neutralize the undesirable stimulating effects sometimes associated with ephedrine-like drugs and theophylline derivatives as well as the depression sometimes associated with antihistaminic drugs, while the three agents, Nethamine, Butaphyllamine, and Decapryn, combine to relieve the allergic and asthmatic symptoms.

Although the usual single, oral dose was one capsule or teaspoonful for older children and two for adults, there is considerable latitude in dosage. Many adults respond well to a single capsule, whereas apparent therapeutic failure has resulted from failure to give three or four capsules to patients not relieved promptly by lower dosage. When therapy was continued over a long period of time, it was not necessary to increase the dose.

Patients with severe chronic bronchial asthma who are subject to attacks of status asthmaticus may develop symptoms of such severity that no form of therapy short of intravenous injections of theophylline will give satisfactory relief.[6,7] In such instances, oral therapy should not be continued when it does not give relief. After the attack has subsided following parenteral medication, oral therapy should be resumed.

On the whole, the continued use of Nethaprin was found to be dependent upon the age of the patient, the severity of the symptoms, and especially upon the response of the patient to allergic management. As the patients improved under such a program, drug therapy was required less and less frequently and was ultimately discontinued in a large percentage of cases.

SUMMARY

1. Nethaprin has been used over a two-year period in the symptomatic and palliative treatment of 441 cases of bronchial asthma.
2. The effectiveness in the relief of symptoms has been highly gratifying.
3. Untoward side effects were inconspicuous.
4. The usual single oral dose was one capsule or teaspoonful for older children, two capsules for adults, repeated as needed (usually three times daily).
5. Repeated administration has not necessitated an increase in dosage.

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(Continued on Page 776)

AIR-CONTAMINANT SURVEY OF SANTA BARBARA, CALIFORNIA (1947-1948)

HILDAHL I. BURTNESS, M.D., and SONIA E. ALLEN, A.B.
The Sansum Clinic
Santa Barbara, California

INVESTIGATION of the literature shows that there have been several excellent studies of both pollen and fungus contaminants in the air for various areas on the Pacific coast. However, such a study does not appear to have been made in Santa Barbara County, and this survey was undertaken to determine the contaminants present, the abundance of their occurrence, and any seasonal variations.

Pollen studies were made with the emulsion-covered slide, exposure being made on top of a three-story building in the center of Santa Barbara valley. As Santa Barbara lies between the Santa Ynez mountains and the ocean, this seemed a central location. The prevailing wind here is from the south, and the average velocity is about 13 miles per hour. The average rainfall in this area is about 18 inches, although during the two years of this study the total fall each year was less than one-half this amount. The slides were read over a one-inch square surface, after a 24-hour exposure in a sheltered holder, and results were tabulated on a weekly basis. The weekly figures are used, as these give larger and more easily observed differences on both table and graph.

Fungus investigation was twofold, both the slide and plate methods being used. However, the same problem arose that has been encountered elsewhere in this connection—no correlation being found between the slide and the plate counts. Although both are recorded, the plate count seems the more reliable in that many of the colonies are not identifiable on the slide, while only the rusts and smuts fail to grow on the plates. Standard petri dishes were used, being covered with Sabouraud's agar the first year and the special medium being used in the national fungus survey the second year. The plates were exposed on a shelf extending out from the second-story window ledge on the west side of the same building where the slides were exposed. Again results are tabulated on a weekly basis, the daily exposure being 12 minutes in the early morning.

Two facts stand out in the pollen study. First, the abundance of pollens in the spring is very marked here, due largely to Quercus and Pinus, supplemented the first year at least by a very large Cupressus showing. Although neither Pinus nor Cupressus is found to be the chief cause of hay fever in many cases, the volume here makes them significant, especially as they fall so near the period of the more frequently troublesome Quercus. In contrast to other areas, the fall count is very low; in fact, the low count of ragweed is surprising in the light of the known area of ragweed stands in this county. No attempt has been made to correlate

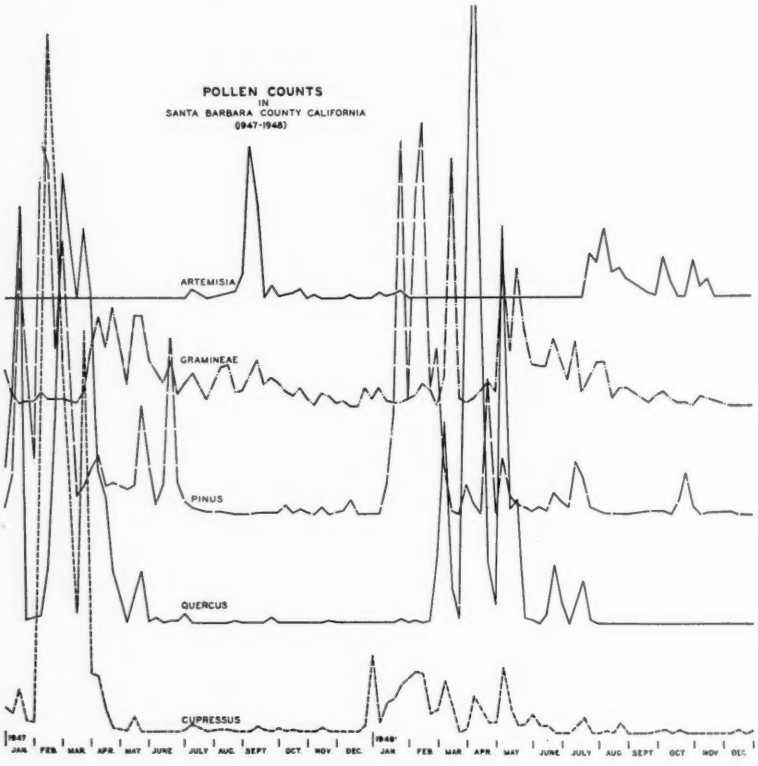

Fig. 1.

TABLE I. POLLEN COUNTS IN SANTA BARBARA, CALIFORNIA

1947 (entire year)		1948 (entire year)	
1. Quercus	1,675	1. Quercus	1,285
2. Cupressus	1,573	2. Pinus	1,222
3. Pinus	1,263	3. Gramineae	763
4. Gramineae	682	4. Adenostoma	410
5. Schinus	314	5. Cupressus	322
6. Eucalyptus	261	6. Olea	301
7. Artemisia	181	7. Artemisia	200
8. Alnus	118	8. Cocos	155
9. Juglans	116	9. Eucalyptus	143
10. Cocos	96	10. Chenopodium	104
11. Acacia	88	11. Juglans	71
12. Compositae	51	12. Alnus	70
13. Populus	36	13. Populus	68
14. Ambrosia	35	14. Acacia	21
15. Olea	29	15. Ambrosia	13
16. Chenopodium	24	16. Compositae	11
17. Adenostoma	19	17. Schinus	2
18. Ligustrum	3		
Unknown	140	Unknown	153

the actual pollen count with the known growth standing in the county, but this obvious lack of pollen brought this question to our attention. The other outstanding fall pollen found in the surveys south of here, Artemisia, is

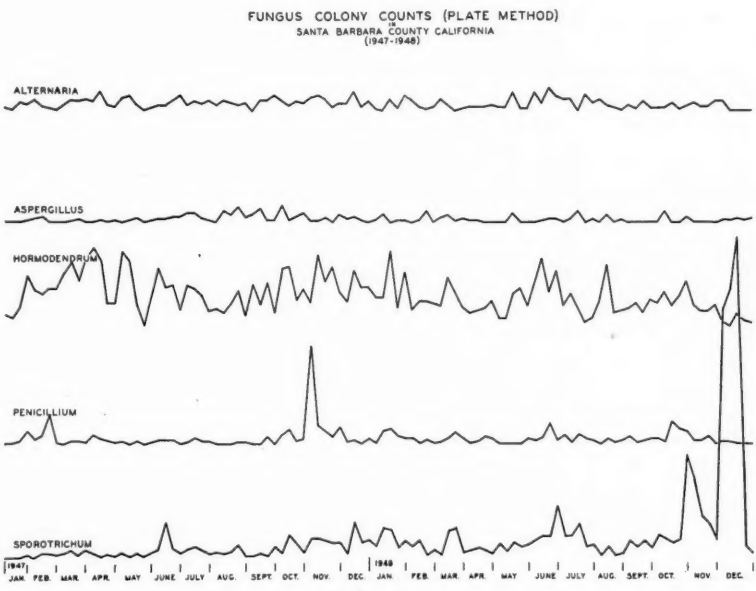

Fig. 2.

TABLE II. FUNGUS COLONY COUNTS IN SANTA BARBARA, CALIFORNIA
(Plate Method)

	1947 (entire year)		1948 (entire year)	
1.	Hormodendrum	1,225	Hormodendrum	891
2.	Alternaria	217	Sporotrichum	890
3.	Penicillium	200	Alternaria	173
4.	Sporotrichum	183	Penicillium	142
5.	Aspergillus	107	Epicoccum	85
6.	Epicoccum	68	Stemphyllium	68
7.	Stemphyllium	67	Aspergillus	67
8.	Macrosporium	51	Macrosporium	50
9.	Botrytis	29	Botrytis	28
10.	Chaetomium	13	Helminthosporium	18
11.	Pleospora	10	Mucor	7
12.	Mucor	9	Pleospora	6
13.	Helminthosporium	9	Rhizopus	4
14.	Rhizopus	5	Chaetomium	0
	Unknown	312	Unknown	294

TABLE III. FUNGUS SPORE COUNTS IN SANTA BARBARA, CALIFORNIA
(Slide Method)

	1947 (entire year)		1948 (entire year)	
1.	Alternaria	765	Alternaria	495
2.	Rusts	444	Rusts	453
3.	Stemphyllium	273	Macrosporium	185
4.	Smuts	166	Stemphyllium	128
5.	Macrosporium	156	Smuts	114
6.	Hormodendrum	144	Helminthosporium	81
7.	Helminthosporium	61	Hormodendrum	75
	Unknown	76	Unknown	97

also lower than would be expected. In the light of the fact that this study was made in two of the driest years that this county has ever known, it will be interesting to see the count that is obtained in more normal years, especially in these two genera: Ambrosia and Artemisia.

The most commonly occurring pollens found here are shown in Table I. As can be seen, Quercus and Pinus are so abundant as to warrant comparison with other genera found in large amounts elsewhere. Quercus is found to be two and one-half times as abundant as Gramineae, even though Gramineae is found in nearly every month of the year, while the bulk of the Quercus pollen was found in the first four months of the year.

The findings in the study of the fungi follow that of other surveys more nearly in that Hormodendrum colonies outnumber those of other groups rather markedly, as shown in Table II and Table III. The Alternaria group is second in frequency, and if all its member counts are combined, we still find that there were four times as many Hormodendrum as Alternaria group colonies in 1947 and three times as many in 1948. The Alternaria group count, however, was rather consistent over the two-year period, while the Hormodendrum count was 30 per cent more the first year than in the second year. On the other hand, the Sporotrichum count was much higher here than elsewhere. This count was much higher during 1948 than in 1947, more than one-third of this figure being found in a three-day splatter of colonies during a three-week period.

Alternaria is more prevalent here than in the San Francisco study by Deamer in 1947, and Rhizopus and Penicillium show much less importance than found by Schonwald in Seattle. Penicillium is well represented here, however, though the count is not as high as found at the beaches in San Diego County.

The accompanying tables and graphs show the frequency and distribution of occurrence of both pollen and fungus spore counts. It will be noted that an abundance of Rust spores is shown on the slide counts and these are often correlated with the increased showing of grass pollen.

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317 West Pueblo Street,
Santa Barbara, California

SEVERE SERUM-SICKNESS TYPE OF PENICILLIN REACTION

Failure of Antihistaminic Therapy

BERNARD M. ZUSSMAN, M.D., F.A.C.A.

Memphis, Tennessee

THIS PAPER is being written, not to add another case report to the voluminous literature about this subject, but to pause for a moment in our mad rush to sensitize an entire population, ourselves included. Since 1943, the literature has abounded with new and interesting forms of penicillin sensitivities, and, with the introduction of the antihistaminic drugs, we all heaved a sigh of relief at the relative ease with which these reactions could be controlled. However, there is an accumulating literature on reactive cases of an unusually severe nature, resisting every kind of antihistaminic drug, and the following is reported as one of this type.

CASE REPORT

The patient, a 34-year-old physician, had been given three injections of 300,000 units of procaine penicillin G in oil (Duracillin) for the treatment of a minor hand injury. Approximately ten days later, he broke out with giant urticaria which rapidly extended over his entire body, including the scalp. His face and eyes were swollen, and the itching was intense. He was given 0.3 cc epinephrine, which was repeated at intervals of two to three hours, and was started on Benadryl 50 mg every four hours and nembutal grains 3. The following day, as the patient's condition appeared worse, he was started on Hydrillin 100 mg and advised to use a 2 per cent Pyribenzamine ointment (Ciba). In addition to the generalized urticaria and edema, there were severe headache, polyarthralgia and slight neck rigidity. The patient appeared very ill, temperature 102° and pulse 120. A curious phenomenon noted was that when patient lowered his legs over the side of bed, they became painful and white. This was attributed to interference with the circulation to the legs caused by pressure on the arteries by the edematous reaction, resulting in local ischemia. As the two previous antihistaminic drugs appeared of no avail, a third, Pyribenzamine 100 mg. every four hours, was tried. In addition he was given 50 mg nicotinic acid dissolved in 10 cc distilled water intravenously, which appeared to afford temporary relief. That night the patient's condition appeared even worse, and it was necessary to resort to morphine sulfate ¼ gr to give some fitful relief.

Starch baths, 50 per cent glucose intravenously and a fourth antihistaminic, Neo-antergan 100 mg was tried. By now the patient had been ill for five days and it was felt that the allergic reaction might subside spontaneously by this time.

After three or four doses of Neo-antergan, the patient stated that he felt much better, and his urticaria appeared to be diminishing. Whether or not this was coincidental with a spontaneous remission of the allergic reaction is conjectural. At any rate by the next (sixth) day his rash was completely gone and he was discharged.

DISCUSSION

The number of cases in which the antihistaminic agents do not have any effect are rarely reported. Following is a brief survey of the recent litera-

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ture showing the failure of drug therapy in penicillin reactions of the serum sickness type. Davis[4] reported two cases of severe urticarial delayed reactions following intramuscular penicillin in which no appreciable benefit was obtained from Benadryl or from the sympathomimetic drugs. He also states that he has seen eight moderately severe urticarial reactions following oral administration in which Benadryl, et cetera, failed to relieve the symptoms in two of the delayed serum sickness types. One of his cases had urticaria and pruritus for twenty-eight days despite all therapy before the symptoms finally subsided. Friedlaender[6] reported a case of urticaria, polyarthritis, and severe generalized edema following penicillin, in which Benadryl was unable to control the polyarthritis but did benefit the other symptoms. He suggested that histamine might play a greater rôle in urticaria than in other allergic manifestations, because it responded more readily to the antihistaminic drugs. Kendig and Toone[8] report three cases of delayed serum sickness type of reaction following penicillin. In one case, Benadryl gave little relief from symptoms due to the urticaria which lasted for two weeks. Two of their cases had previously received penicillin, and these authors felt that subsequent courses of penicillin therapy increase the hazards of sensitization. Watson[11] reports a case of delayed serum sickness type of reaction on the ninth day following 250,000 units of aqueous penicillin for three successive days. This patient had severe pruritus and urticaria which was not relieved by Benadryl or epinephrine in full therapeutic dosage and which lasted for seven days. Wilcox reports a case of urticaria following penicillin therapy in which the concomitant use of Benadryl and epinephrine caused collapse and both drugs had to be discontinued.

That the method of administration has nothing to do with the allergic reactions to penicillin has been shown by the work of Barach,[1] who used penicillin aerosol in ninety-one courses of penicillin therapy in sixty asthmatic patients (some of this may have been given systemically): "Reactions to penicillin necessitating interruption of therapy occurred during twenty-four of the ninety-one courses. Exacerbation of asthma was seen in fifteen patients, urticaria in ten, reddened tongue in seven, and fever and swollen joints in one." Gordon[7] reported three cases of delayed serum-sickness reactions to penicillin therapy, two of which had penicillin previously. He stated that the disease ran a self-limited course of seven to ten days, regardless of the type of therapy employed. Brown[2] states that, in his personal experience with urticaria and angioneurotic edema following procaine penicillin G in peanut oil, no alleviation of symptoms occurred following 500 and 100 mg doses of Pyribenzamine, Thephorin, Thenylene, Neohetramine, or Decapryn, with mild alleviation following ingestion of Trimeton. He states that Demerol in 50 to 100 mg doses controlled the associated pruritus, but had no effect on the urticaria or edema.

That delayed type of serum-sickness reactions may end fatally is seen in the case reported by Wilensky,[12] whose patient had received 720,000 units of penicillin following resection for gastric carcinoma. On the sixth postoperative day, he developed vomiting, fever of 104° and a scarlatiniform rash which became urticarial on the following day. Despite immediate cessation of penicillin and substitution of sulfadiazine, the patient's condition rapidly deteriorated and he died. No mention of antihistaminic therapy was made, and the mechanism of the patient's death was explained on the basis of delayed anaphylactic shock as reported. Since then, several other fatalities have been reported following penicillin therapy: in one,

as a result of acute edema of larynx and in the other, as a result of acute anaphylactic shock following an injection of penicillin which was thought to have entered a vein, as reported by G. L. Waldbott.[10]

CLASSIFICATION OF SERUM-SICKNESS REACTIONS

1. The *delayed serum-sickness type of response* usually follows within seven to ten days after the primary injection, though delayed responses as long as thirty to forty-five days have been reported.
2. *Accelerated serum sickness* occurs after a much shortened interval, from several hours to several days. This type of response generally follows a second injection of serum whether or not the primary injection was followed by clinical manifestations of serum sickness. The symptoms of the accelerated type resemble those of ordinary serum sickness but are likely to be more violent.
3. *Local serum sickness:* In some cases there is no generalized reaction but merely local swelling and tenderness at the site of injection. In other cases, the local reaction precedes the general eruption by one or more days.

PATHOGENESIS OF SERUM-SICKNESS TYPE OF PENICILLIN REACTION

The term serum sickness or serum disease was originally applied by Von Pirquet to the familiar sequellae which followed by a number of days an injection of foreign serum. Horse serum is the most common serum used, although serum from other animals (hogs, sheep, rabbit, et cetera) can and do produce serum sickness. However, since the turn of the century, the use of parenterally administered extracts has been accompanied by a markedly increased incidence of allergic reactions. Injectable vitamin products, sclerosing fluids, organic extracts (liver, insulin, glandular preparations, vaccines, toxoids, drugs, and antibiotics) constitute a formidable group of materials to which the patient can become sensitive. The development of antibiotics and chemotherapeutic drugs has been a two-edged sword. "It is well, however, in this connection, to remember that sensitivity to the chemicals may become increasingly important as their use increases and opportunity is given for sensitization to them to develop."[3]

That severe irreversible tissue destruction may follow serum sickness has been proven by the epic work of Rich and Gregory[5] in which they demonstrated the typical lesions of periarteritis nodosa in patients who died following serum sickness or allergic reactions to sulfonamides. Furthermore, they were able to reproduce these same lesions in experimental animals following single and repeated doses of foreign serum to cause serum sickness. Recently, the sensitizing properties of penicillin have been studied by McClosky and Smith,[9] who demonstrated anaphylactic sensitization in guinea pigs with repeated small doses of commercial penicillin.

CONCLUSION

1. Penicillin given by oral ingestion, topical application, aerosol inhalation, or by injection sensitize a certain per cent of the population.
2. Allergic reactions occur most frequently in patients who have had several courses of penicillin and the incidence is definitely on the increase.
3. The antihistaminic drugs frequently are unsuccesful in controlling these penicillin reactions, especially the more severe ones.
4. Skin tests are unreliable in predicting the occurrence of reactions which may be fatal.

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MARITAL ADJUSTMENTS IN THE PARENTS OF ALLERGIC CHILDREN

HYMAN MILLER, M.D., F.A.C.A., and DOROTHY W. BARUCH, Ph.D.
Beverly Hills, California

THE PRESENT paper reports on one phase of a continuing study of the psychosomatic aspects of allergy which has shown the emergence of a characteristic dynamic pattern in allergic individuals. Of primary importance in this pattern is the emotional interaction between mother and child.

Generally, it is the mother who determines the emotional climate in which any child finds himself. The child's dynamic pattern varies with this climate. His wholesome development depends on the presence of maternal love. But, as pointed out by many observers, maternal love is not always forthcoming. Some children are raised in a climate of maternal rejection.[8,12,13]

Resentment is every child's normal and healthy reaction to insufficient love from his mother. This resentment can be expressed outwardly, or its outward expression can be held in and blocked. In any case, it creates psychic energy which must be discharged. The nonallergic child characteristically discharges resentment which he feels against his parents by bringing it out quite directly against his parents in manifest misbehavior that annoys or aggravates them. On the other hand, the allergic child characteristically is unable to bring resentment out as directly. In him there is a block to such frankness. The hostility he feels against his parents is repressed. But the psychic energy of the hostility must be discharged. This he tries to accomplish through physical symptoms. The physical symptoms are used then to express, in masked fashion, the hostility generated by the need for more love. They also cry for more love.[4]

The allergic child is hungry for love and he is inordinately full of anxiety. He fantasies and fears losing his mother. As shown in another study, the first onset of his symptoms often follows traumatic episodes which to him stand for the loss of his mother.[9] In these children, the fear of such loss then seems to arise from the experience of maternal rejection.

A high proportion of allergic children live in a climate of maternal rejection. The climate may be set even prior to the child's birth.[11] Our sample now contains one hundred allergic children studied physically and psychologically.[10] Of the one hundred children, ninety-seven were rejected (97 per cent). Only three were not.

In a control group of sixty nonallergic children similarly studied, twenty-two children were rejected (36.7 per cent). In comparison with the allergic group, this gives a highly significant critical ratio of 9:4, indicating that the chances for the allergic child's being found in the climate of maternal rejection is far greater than for the nonallergic child.

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Maternal rejection of the allergic child is a basic element in the onset, persistence, and curability of his symptoms. In consequence it is essential not only to recognize the rejection, but also to accept the rejecting mother as sympathetically as the rejected child. Abhorrent as our culture and our own culturally induced attitude make it seem, maternal rejection has its own precursors just as any illness has its precursors. Therefore, it becomes not only important but useful to gain whatever insight we can into the etiology of maternal rejection.

A rejecting attitude toward a child is not an isolated phenomenon in the maternal personality. It is only one manifestation of a complex emotional pattern. Diverse manifestations of the pattern may be exhibited in relationships with other members of the family and with the outside world.

Studies have indicated that a rejecting attitude toward the children goes hand in hand with a poor marriage relationship.[3,5,6,12,13] The marriage relationship, in turn, has been found to be influenced by sexual adjustment.[2,7] Dickinson, for instance, says, "Complete unity in marriage depends on sexual unity." He states that discord over relatives, money, work, management of the children and the home are secondary to sexual conflict. He relates satisfactory sexual adjustment to the achievement of orgasm by both partners.

Since sexual maladjustment is the same entity whether it appears in the family of an allergic child or in the family of a nonallergic child, the data on sexual relationships in the two groups were combined. In our study, we had information on sexual adjustment in 141 cases.

Also, since rejection is the same entity whether it appears in the mother of an allergic child or in the mother of a nonallergic child, for purposes of the present paper the rejecting mothers in both groups were combined. There were evidences of rejecting attitudes in 119 mothers.

Sexual maladjustment was expressed in dissatisfaction concerning such items as the partner's impotence, premature ejaculation, demands for too frequent intercourse, a lack of interest and too infrequent demands, or demands for what the woman termed "unnatural sex practices." But in far greater number, sexual maladjustment was admitted in terms of the woman's own dislike of intercourse accompanied by lack of orgasm.

On this basis, in the 141 cases, 103 women admitted to sexual maladjustment; thirty-eight (27 per cent) claimed they were well adjusted.

Of the 103 women in the maladjusted group, eighty-seven (84 per cent) were rejecting mothers. Sixteen (16 per cent) were not rejecting. The highly significant critical ratio of 13:7 indicates that where sexual maladjustment was present, there was a significantly higher incidence of maternal rejection.

Of the 119 rejecting mothers, information regarding sexual adjustment was available on 101. Of these, eighty-seven (86 per cent) admitted to sexual maladjustment; fourteen (14 per cent) claimed they were well

adjusted. The highly significant critical ratio of 14:7 indicates that among rejecting mothers there is a significantly higher degree of sexual maladjustment than among nonrejecting mothers.

But the marriage is not the only precursor to be considered. Studies such as those by Despres,[1] Figge,[3] Newell,[12,13] Stein,[14] Symonds[15] and Wolberg[16] have shown that the marriage does play a part in the formation of the rejecting attitude. But so also do the mother's own childhood experiences play a part.

In our patients this was confirmed.

The following cases illustrate, in brief, how the mother's childhood influences her marriage, her attitude toward her children, and even her husband's relationship with the children.

Mrs. D. was a woman in her early thirties. In spite of an outwardly quiet maternal concern, she conveyed a feeling of inner desperation and apologetic resentfulness. Her two-year-old boy had recently developed asthma. Of him she said, "He drives me crazy. He wears me out. Life hasn't been easy since I've had him. I'd never have had him if I'd known."

In her own life she had been and still was greatly dependent on her mother. Whenever her child got sick, she called her mother before calling the doctor. She frequently left the child in her mother's care during the day. When she first came into group therapy, she could only express appreciation of her mother's helpfulness. Later, she betrayed glimpses of deep feelings of resentment toward her mother, who she felt had never really cared about her. Of these feelings, she was greatly ashamed. She would repeatedly retract and cover them over with renewed praise.

In contrast, she "worshipped" her father. His last illness had occurred during her pregnancy with the patient. In spite of her pregnancy she took over his care, lifting his paralyzed body and attending to his physical needs. "He wanted me, not my mother, because I was his favorite," she explained. "Being pregnant made it terribly hard. But I managed all the same."

In her marriage, she had quite apparently sought to find another father. She had married a divorced man eighteen years her senior. "He reminded me so much of my father," she said. Sexual adjustment was poor and she never attained orgasm. Unconscious oedipal feelings were apparently too much in the way. In an attempt to resolve the inner conflict, she renounced sexual contact on religious grounds.

She felt so "nervous," however, that she continuously tried to get her husband to take over the child's care during evenings and nights when he was ill. In passive, escapist fashion, the husband evaded this responsibility, drinking to excess and staying away from home.

Thus the child got neither the mother's love nor the father's. In his asthmatic attacks, he constantly cried to be held.

* * *

Mrs. S., a woman of twenty-four, characteristically covered her feelings with an air of flippancy. However, when she spoke of her three-year-old allergic girl, she suddenly gave way to a strong onrush of feeling. "I actually felt I could kill her," she said. "I wanted to throw her against the wall and bash her brains out."

Her own mother had died in Mrs. S.'s adolescence. Her death made it especially difficult for Mrs. S. to admit the ambivalence toward her which gradually came out in the therapy group. She would say of her mother, "She really never loved

me. She would punish me terribly. She'd tell me all the time not to be bad. I was afraid to do anything. But—she really was good to me."

With her father, she recalled some intimate scenes. She recounted, with excited embarrassment, that after her mother died, she had shown herself off to him in her slip and he had fondled her breasts.

When her father remarried, she resented her stepmother and ran away to the home of the man whom she subsequently married. Obviously putting him in her father's place, she sought to have him take care of her. As he said in an interview, "I've been a father to her. I've had a rough time being a boy friend and a father both."

Their sexual adjustment was poor. She never experienced orgasm.

In the therapy group which she entered, the death wishes she had expressed in the beginning toward her child were ultimately related to her death wishes to her mother. Just as she had earlier tried to prove herself a loving daughter, she had later tried to prove herself a loving mother.

In spite of rejecting her child, she would not let her husband have anything to do with the child's care. When he demanded that he had a right to take part in it, she would pack up and leave, taking the child along, only to return when the care grew too burdensome.

In this unstable environment, the child could gain adequate love from neither and felt lost and insecure.

* * *

When Mrs. G. first entered therapy with her asthmatic boy of seven, she, too, was dependent on her mother, turning to her continuously for help and advice. Bit by bit, with great guilt apparent, she brought her deeper feelings out. She gave a picture of her mother as too busy, too burdened, having failed to take time even to gather the family around the dinner table. Mrs. G. recalled herself as a child, standing at the kitchen sink, eating alone, feeling shut off and rejected.

In her early years her father had had a psychotic episode. This had been preceded by frank sex play with his daughter which she enjoyed until it ended in an attempt at rape.

In her marriage she found it difficult to achieve complete sexual adjustment. She had chosen a husband whose quiet, contained personality gave promise of the dependability she had always craved from her father. Actually her husband was quite immature. This left her disappointed and with greater responsibility than she felt able to shoulder. She swung back and forth between attempts to do more than her share for the child and attempts to get her husband to take over. Fundamentally, however, she rejected her child. In her therapy she came upon a fantasy that had hitherto lain unconscious—in her own words, that her child "was the product of an incestuous union" with her own father. The pressure of this in her unconscious had created such a guilt that it had contributed to the rejection of her child. Even so she managed to cover the rejection with the same excessive devotion she had used in covering her earlier animosity to her mother.

Again in this case, the child felt a lack of both maternal and paternal emotional support.

* * *

Mrs. A., the mother of a twelve-year-old asthmatic daughter, herself had a mother whom she felt was conscientious but without spontaneous good humor or warmth. Even so, Mrs. A. had pinned a picture of a devoted mother over her inner picture of the rejecting mother whom she resented.

With her father Mrs. A. had "more in common." "He was a good man, upright and moral," she stated with pride. She married a man the essence of uprightness and morality, over fifteen years older than herself. Their sexual adjustment was poor.

Mrs. A. progressively turned more and more of her daughter's care over to her

husband. He met this responsibility by making great demands for perfectionistic achievement which the girl could not meet. Mrs. A. finally ended by divorcing her husband and leaving the child under his repressive domination.

* * *

Mrs. F., the mother of two allergic girls with asthma and eczema, met life with starry-eyed romantic unrealism. Her father and mother had separated when she was small and she had not seen her father again until her late adolescence. Her mother had alternately deposited her with her maternal grandmother or had taken her traveling with a governess in immediate charge. Only after several months of individual therapy did Mrs. F. glimpse the "murderous" impulses toward her mother which lay behind her fawning façade.

Her father she remembered as a prince charming, "full of fun." When she was in her teens her mother remarried and she turned with passionate devotion to the stepfather, looking to him for the steadiness, stability and love she had missed.

In her own marriage, she sought to recapture the prince charming of her childhood. Her husband was "glamourous, tall and handsome. Full of fun."

Sex, she said, was not important. "I'm not very much that way. I really care more about affection than about sex."

Her children were unanticipated and unwelcome. The fairy prince turned out to be a play-boy. He failed to take responsibility and the marriage ended in divorce. Mrs. F. then packed up and removed the children altogether from contact with their father, traveling to a distant city to live near her stepfather on whom in spite of his disdain she continued to lean for guidance and advice.

Again her children had neither father nor mother on whom they could rely to meet their emotional needs.

From these and other cases several repetitive themes appeared which suggest a pattern in the lives of these rejecting mothers which will bear further investigation.

1. In their childhood these mothers felt deprived of their own mother's affection. They unconsciously betrayed that they felt rejected.

2. Resentment to their mothers appeared to be more intense and more deeply repressed than in women who were not rejecting. By the same token, they were apprehensive about going counter to their mothers' wishes. They showed more marked dependency and maintained more obedient devotion.

3. They fled from the awareness of their hostility to their mothers. In therapy, with the slightest dawning of such awareness, they were prone to retract quickly and once more to cover over.

4. They reënacted their relationship with their mothers in their relationship with their children. Instead of the child's being a person to whom they owed devotion, the child became a person who made demands.

5. The hostility felt to their mothers was duplicated in the hostility felt to their children. So great was the resultant pressure that in general they found it harder than other mothers to brook any expression of hostility from the child lest it act as a trigger to their own pent-up store.

6. To avoid the danger of losing control of themselves, they curbed their children's hostility by excessive restrictions, care and demands.

7. There were marked unresolved oedipal feelings in these mothers which

earlier had augmented the animosity toward their mothers and later had influenced their choice of a husband.

8. In several cases (as in Mrs. G's.) material brought out by the mother suggested that the child had unconsciously been fantasied as the child of the mother's father. The ensuing guilt then had brought further impulsion for the mother to deny her child.

9. The sexual adjustment of these women was ordinarily poor with orgasm usually lacking or sex drive inadequate and low.

Basically, these women were deprived, insecure individuals evidencing an unreadiness and inability to assume a mature sexual and maternal rôle. The rejecting mother comes with her own childhood experiences into her marriage. Her marriage, in turn, may either activate or aggravate conflicts which were born in the past. In its turn, marriage may bring experiences which are unbearable either of themselves or because of her set from the past. These may add to her own feeling of insecurity. Both present and past color her feelings toward her husband. They color her feelings toward her children. Subtly, or otherwise, they influence the relationship which her husband has with the children and the child's conflicts out of which his somatic symptoms may arise.

In our sample, in general, the interaction between husband and wife and its influence on the father-child relationship seemed to fall into four patterns:

1. The mother, because of her desire to avoid a mother rôle, made demands that the father take over the responsibility of the child. He either acceded with resentment or he escaped into immersion in work, drinking, and the like.

2. The mother, because of her unconscious drive to prove herself a good mother to cover her inner rejection, pushed the father away from the children. This ended either in conflict or in the father's acceding.

3. The mother chose a husband so immature in his own development that he failed to assume a father rôle. This left the mother holding unwelcome responsibility added to at times by casting the father in the rôle of another burdensome child.

4. In a few cases, the father assumed an oversolicitous rôle, attempting to make up for his wife's failure, which he unconsciously resented but did not wish to admit. This, the child felt, and, as a result, the father also failed in furnishing the emotional security which the child should have had.

In conclusion, it may be said that a mother's rejecting attitude is a product of many factors for which she is no more responsible than the allergic child is responsible for his clinical symptoms. Her suffering is as real as her child's. Our cultural standards cause her attitude to be as repugnant to herself as it is to the society which sets the standards for her. Our culture condemns her for an attitude which is of its own making. As one understands the factors that enter into a mother's rejecting attitude,

it becomes possible to treat both mother and child with greater sympathy and skill.

SUMMARY

1. In this, as in previous studies, maternal rejection is seen as an important item in the emotional climate of the allergic child's environment.

2. In its etiology, maternal rejection is found to be related to the mother's emotional immaturity, a product of her own life history.

3. Of primary importance are the mother's rejection by her own mother, the unresolved oedipal attachment to her father, and the hostility to her mother derived from both.

4. As a result of childhood conflict, sexual adjustment in the marriage of these women is poor.

5. Statistically, poor sexual adjustment is significantly related to maternal rejection.

6. The influence on father-child relationship is discussed.

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201 S. Lasky Drive

MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

XIV. Fungi in Aerobiological Populations. The Fungus Flora of Tillandsia Species (Ball and Spanish Moss)

MARIE BETZNER MORROW, Ph.D., and EDNA CRONQUIST WHEELER, M.A.
Austin, Texas

PHENOMENAL interest in the subject of fungi in relation to inhalant allergy has developed in the last twenty-five years. Since 1925, when Van Leeuwen proposed that air-borne mold spores were a cause of inhalant allergy in Holland, an increasing number of workers here and abroad have contributed to our present knowledge concerning the allergenicity of molds and other fungi. During this time an increasing interest has been indicated in the possibility that the so-called "epiphytic mosses," which are not mosses at all, but members of the pineapple family (Bromeliaceae), as represented by "ball moss" (*Tillandsia recurvata* Linn.) and "Spanish moss" (*Tillandsia usneoides* Linn.), may bear some relation to the incidence of inhalant respiratory allergy. This is particularly true in those sections of the southern United States and elsewhere where these species are found in more or less profusion. In this paper the word "moss" will be used for these epiphytic bromeliads, and the phrase "ball moss" and "Spanish moss," for *Tillandsia recurvata* and *Tillandsia usneoides*, respectively.

Some studies have been reported on these mosses with respect to their allergenic properties, but nothing was done with the fungi, nor were they mentioned as contributing factors. Fifty patients in Florida[3] were tested for sensitivity to the pollen and to the ground fiber of the plant, with negative results in both cases. On the other hand, positive results were reported in New York[2] with the extracts of new, unused Spanish moss as employed in furniture upholstering, and also with the ground new moss insufflated into the patient's nostril. It was implied that this sensitivity was due to the moss material itself, but it could be explained by fungi or other extraneous substances present, since the moss material was not sterilized. New material was used in order to reduce the possibility of contamination, where contamination connotes anything that might get into the material during use, and without considering the possibility of fungi and other extraneous substances that might be associated with the new, unused moss material.

It has been apparent for some time to physicians, mycologists, plant pathologists, and others, whose interests extend into this field, that detailed studies of these bromeliads as potential hazards for sensitive individuals from the standpoint of the fungi present was desirable, and

From The University of Texas.
Dr. Morrow is an Honorary Fellow of The American College of Allergists.
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would be forthcoming. The fact that both ball and Spanish moss are found in and around Austin, Texas, was a determining factor in undertaking the present investigation at The University of Texas. Also, an exploratory study of these had been made earlier (Lowe and Morrow, 1939).

The present studies were planned for the purpose of finding out what relations, if any, exist between the presence of ball and Spanish moss plants in a given location or environment, and the air population at that location; and whether the presence of these two plants in a given location indicates a potential source of allergenic material in the air population there; and whether these plants, by implication, therefore constitute a potential hazard with respect to inhalant respiratory diseases, and as such, should be investigated in analyzing an environment for sensitive individuals. Three objectives were apparent. One was to determine what fungi, if any, are present on ball and Spanish moss in a natural habitat. A second was to determine, in so far as possible, whether the fungi present on the living plants are a part of the fungus population found generally in that environment, that is, on other substrates, or whether these are confined to the moss plants, and thereby constitute a moss flora. Finally, a third objective was to determine whether the fungi on the respective moss plants are generally air-borne, as indicated by their presence on adhesive slides and culture plates exposed in the same environment.

Ball moss (*T. recurvata*) which grows in gray-green spherical tufts on some twenty-five tree species from Florida to Argentina and Chile, and the hoary-gray Spanish moss (*T. usneoides*) which hangs in pendulous festoons from a number of trees extending into tropical America and southward into Brazil, are among the most characteristic plants of our southern regions.

The Tillandsia mosses, which are always epiphytic, and never parasitic or saprophytic, are perennial herbs with no roots, but absorb moisture through the tiny scales that cover the leaves and stems. The necessary minerals are present in the rain and in the dust from the air which collect in and among the scales of the plants. It was taken more or less for granted that these scaly surfaces were also substrates for fungus spores and mycelial fragments. As a matter of fact, fungus pathogens and other organisms associated with Tillandsia species have been described (*Psilonia cylindrospora, Volutella cylindrospora* and *Colleotrichum bromeliacearum*).[5] Without rushing the discussion of the results, it might be said here that none of these was encountered in the present studies.

Although it has been reported that Spanish moss is found mostly on lowland timber, and ball moss on upland timber,[1] these two species are found commonly on cedar elm (*Ulmus crassifolia* Nutt.) in the Austin region; in fact, the two are frequently found on the same tree. For this reason, cedar elm was selected as the tree source of both mosses in these experiments. Parasites on cedar elm have also been listed (*Cylindro-*

sporium tenuisporium, Gleosporium ulmeum, Gnomia usnea and *Urnula geaster*).[5] These, likewise, were not recovered.

Ball moss and Spanish moss, together with the cedar elm, were studied as the living substrates. In order to determine whether the fungi isolated from the living plants are specific for these sources, or whether similar fungi might also be found on other substrates in the same environment, other surfaces were examined: namely, sterile ball moss, sterile Spanish moss, sterile filter paper, and sterile cheese cloth. These were placed in the same environment with the living moss plants for a period of ten to twenty days before examination. In the results, the living plants are designated as "normal," the other materials as "sterile."

At the same time that the living substrates and the corresponding other materials were sampled, air exposures were made in the same environment, so as to determine whether the fungi isolated from the different surfaces were also air-borne.

Dilution and direct plating were employed for the study of the substrates, and agar plates were exposed to sample the air population for air-borne fungi. The direct method included direct plating of portions of the substrates unwashed (unW) and washed (W), and the corresponding washings (Wg).

The agar plates were exposed for two-minute intervals. The number of fungi isolated from a two-minute exposure plate, when multiplied by the factor 21,[4] gives a figure comparable to a twenty-four-hour pollen count which is standard in aerobiological analysis.

Three experiments were designed so as to compare the same location at different dates, and to compare different locations within the city. Experiment 1. West 22nd Street; beginning February 29, 1944; sampled March 11. Experiment 2. West 22nd Street; beginning April 4, 1944; sampled April 17. Experiment 3. Windsor Road; beginning April 10, 1944; sampled April 29.

The results presented in this paper consist of the outstanding facts revealed in the studies which lend themselves to a short paper, and are presented in summary form. Details of method, qualitative and quantitative tables, lists, figures, graphs, photographs, and other details, while invaluable for a record, are omitted here, as well as the historic aspects. For the task of collecting and recording a voluminous amount of data, special credit is due the junior author.

Some sixty-five different species of fungi were isolated. About fifty species were isolated from plant material; of these, thirty-five were recovered from living substrates. Thirty-one species were recovered from living mosses, twenty-five from ball moss, sixteen from Spanish moss, and seventeen from cedar elm.

Seven species were isolated only from living substrates; five from mosses, four from ball (*Helminthosporium* sp. No. 46, sterile pale species No. 50 and No. 52, and an undetermined sclerotial-like species No. 40),

and one from Spanish moss (a sterile pale species No. 39); and two from cedar elm (*Phoma* sp. No. 84 and an undetermined pycnidial species No. 71).

The pathogens listed by Seymour (1929)[5] and mentioned by Birge (1911)[1] for mosses as hosts, and those listed by Seymour for cedar elm apparently were not recovered in these experiments. Some of the fungi encountered (*Phoma* sp. No. 84, *Helminthosporium* sp. No. 46, the pycnidial species No. 71, and certain of the other undetermined species), by virtue of being confined to a living substrate, suggest phytopathogens, but they were not indicated as such in this study.

Furthermore, it was not possible to determine whether any of the fungi isolated only from the living mosses were specific to the growing plant. Only one of these (the sterile pale species No. 52) was isolated when plant portions were plated directly. Not any of these were recovered from the washed portions so as to indicate their attachment in some way to the plant tissue.

The dominant fungi included some of the well-known cellulose decomposing genera (*Trichoderma, Chaetomium*) which, when present, may very probably be involved in the natural retting process which is the fate sometimes of these mosses. A number of the dominant fungi were recognized as soil inhabitants which are known to be air-borne.

Most of the dominant fungi encountered throughout the experiments were recovered from the living mosses, but they were also recovered from one or more of the other substrates examined, as well as from the air-exposure plates. At least seven species (*Hormodendrum cladosporioides, Alternaria tenuis, Alternaria humicola,* pale yeasts of the Saccharomyces type, *Aspergillus niger, Fusarium elegans,* and a pycnidial species No. 42) were recovered from all substrates. Four of these (*H. cladosporioides, A. tenuis,* the pale yeasts, and *A. niger*) also appeared on the air-exposure plates. Two of these (*A. niger* and *F. elegans*) were identified with the direct plating; the others appeared more or less consistently in both dilution and direct plates. These cosmopolitan dominants stand out not only because of their universality with respect to substrates, but also because they are found generally in the air populations of the same environments, and, furthermore, because of the high numbers in which they occur when quantitative counts are made.

High counts of the fungi, as well as a relatively large number of species, were identified with the living mosses, but this was particularly striking for the ball moss with the highest total counts (22×10^5) and individual counts of *Hormodendrum cladosporioides* (11×10^5), *Alternaria tenuis* (4×10^5), *Fusarium elegans* (1×10^5), and a *Phoma* species (3.5×10^5). Although the pale yeasts were not included in the total counts, they were recovered from the living ball moss plants in considerably high numbers (17.5×10^5). The occurrence of high counts and a large number of dif-

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CLINICAL OBSERVATIONS IN THE USE OF COMBINED CALCIUM-ANTIHISTAMINE THERAPY IN THE TREATMENT OF URTICARIA

A Preliminary Report

WILLIAM PARKER, M.D.
St. Louis, Missouri

PRIOR to the widespread use of antihistaminic drugs, intravenous calcium therapy was widely used as a method of treatment for urticaria.[3] Experience with this method of treatment varied widely. This may perhaps have been due, at least in part, to the fact that newer treatments for these conditions have constantly appeared in the literature, replacing older treatments and making an investigation less important, especially of late, with the advent of antihistaminic therapy.

In spite of the advance of therapy in this field, the dermatologist is frequently confronted with those cases of urticaria which do not respond even symptomatically to newer methods of treatment, so that he often falls back upon older, discarded methods. Some investigators have recently reported the use of histamine desensitization as a therapy quite contrary to the use of the antihistamine approach.[5,6,7] It is precisely such a group of cases that is included in this report.

This group constitutes twenty such cases. In all, the history was generally similar. The eruption came on acutely, was not preceded by previous attacks, was associated with nervousness, and responded very mildly or not at all to antihistamine therapy. In all cases, attempts to establish a history of allergy proved fruitless, and patch tests or scratch tests, or both, were non-revealing. The twenty cases chosen were singled out particularly for their resemblance to each other, not only subjectively, but objectively as well. Besides the usual generalized eruption of wheals and the presence of dermatographism, there was also an associated arthralgia, with swelling in one or more joints, most commonly involving the ankles, wrists, and knees in that order.

All of these patients were treated by combined calcium and antihistamine intravenous therapy, supported by oral calcium and antihistamine therapy. In all cases, the patients showed the usual response to calcium therapy immediately after completion of the injection—a sensation of severe heat, starting in the throat, and descending progressively to the feet. This was followed by complete relief from itching for various periods, lasting from one hour to three days, with subsidence of lesions, but without complete disappearance. A noteworthy observation in these cases, not found in previous literature, with a subsequent reaction about two hours after the injection, when the patient would suddenly begin to feel slightly nauseated and would develop aches and pains in the affected joints, as

The calcium used in this work was neo-calglucon for the intravenous route, and calcibronat effervescent tablets or granules for oral administration. Neo-calglucon and calcibronat are respectively calcium glucongalactogluconate and calcium-bromido-galactogluconate, which are double salts and maintain their stability without foreign buffers. Neo-calglucon was used because of its high solubility. Calcibronat was used to obtain a mild sedative effect.

The antihistamine used was Benadryl, because of its availability for intravenous use as well as the mild sedative effect when given through either the intravenous or oral route.

well as in the muscles, usually in the upper and lower extremities, along with a sensation of "feverishness" or of feeling "hot and cold" all over the body. These symptoms in about half of the patients were associated with a feeling of weakness, necessitating bed rest. In all cases the symptoms subsided in about three hours and were followed by complete relief from swelling and arthralgia. The wheals, although still present, stopped itching. This freedom from pruritus, in most cases, remained for about three days, and nineteen of the patients reported no recurrences of the swelling or arthralgia. One patient had a recurrence of these symptoms after an upper respiratory infection, one month later, which subsided after a day's treatment of the infection with aureomycin.

REMARKS

Attention is directed to the similarity in response to this treatment by the above-mentioned cases, with the response one obtains with histamine desensitization therapy when the flushing dose is reached, and is followed by similar symptoms. The possible explanation of the above recognized phenomenon may lie in the following: excess histamine has a toxic effect on cell membranes, increasing their permeability and transudation with the clinical manifestations which follow. The antihistaminic agents, by counteracting the histamine, help to allay the phenomenon temporarily. The calcium, by playing a part in normalizing tissue permeability[2,1,4] further helps to allay this phenomenon; hence, this probably accounts for the synergistic effects of the combined therapy. The biochemical and physical functions of calcium, in their relationship to the histamine antihistamine phenomenon, are in need of further investigation, and such investigation may lead to considerable improvement of antihistamine therapy in providing a lead to maintaining permanency of the effects from antihistamine therapy, heretofore lacking.

CONCLUSIONS

1. A preliminary report is made on twenty cases of urticaria, unresponsive to various types of antihistamines alone, but responsive to combined calcium antihistamine therapy.

2. Effects of such combined calcium antihistamine therapy on anaphylactoid reactions associated with urticaria are described.

3. A suggestion for further study of the pharmacodynamics between calcium and the histamine antihistamine phenomenon is made.

REFERENCES

1. Beeson, P. B., and Hoagland, C. L.: Proc. Soc. Exper. Biol. & Med., 38:160, (Feb.) 1938.
2. Blum, E.: Schweiz. Med. Wchnschr., 63:446, (May 13) 1933.
3. Cantarow, A.: Calcium Metabolism and Calcium Therapy. Ed. 2, p. 201. Philadelphia: Lea & Febiger, 1933.
4. Curphey, T. J., and Solomon, S.: New England J. Med., 214:150, (Jan. 23) 1936.
5. Huff, Dick H.: Balyeat Clinic (Oklahoma) Proceedings, 19:6, (June) 1949.
6. Prince, H. E., and Etter, R. L.: Ann. Allergy, 6:386, (July-Aug.) 1948.
7. Strakosh, E. A.: Rocky Mountain M. J., 23:558, (July) 1946.

807 Carleton Building

Preliminary Program

GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

February 9-11, 1951

and

SEVENTH ANNUAL CONGRESS

THE AMERICAN COLLEGE OF ALLERGISTS, INC.

February 11-14, 1951

Edgewater Beach Hotel

Chicago

NOTE: The papers will not necessarily be presented in the order indicated in this preliminary program. The titles of the papers and authors are also subject to change.

JOHN H. MITCHELL, M.D.

Columbus, Ohio

President, 1950-1951

Graduate Instructional Course in Allergy

FRIDAY, FEBRUARY 9, 1951

Morning Session—West Lounge

8:00-9:00 **Registration**

9:00-9:30 **Orientation Lecture for All Registrants**
JOHN D. GILLASPIE, M.D., Boulder, Colorado

9:30-10:00 **Diagnostic Approach**
History-taking
JOHN D. GILLASPIE, M.D., Boulder, Colorado

10:00-12:00 **Skin Tests and Other Tests**
MORRIS KAPLAN, M.D.; NORMAN J. EHRLICH, M.D., A. L. AARONSON, M.D., and Associates, Chicago, Illinois

- Skin Tests
  - Direct
    - Scratch
    - Intracutaneous
    - Puncture
  - Indirect—Passive Transfer
  - Patch
- Other Tests
  - Mucosal
  - Conjunctival
  - Ingestion
  - Inhalation
  - Injection
  - Instillation
  - Physical Allergy
  - Electrophoresis
- Demonstration of Various Methods

12:00-2:00 **LUNCH**

Afternoon Session—West Lounge

DERMATOLOGIC ALLERGY

2:00-2:40 **Pediatric Dermatology**
JEROME GLASER, M.D., Assistant Professor of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York

2:40-3:30 **Atopic Eczema (Adults)**
Neurodermatitis
MORRIS LEIDER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York

3:30-4:20 **Urticaria, Angioneurotic Edema, and Purpura**
NORMAN W. CLEIN, M.D., Children's Clinic; Clinical Assistant Professor of Pediatrics, University of Washington School of Medicine, Seattle, Washington

4:20-5:00 **Eczema Dermatitis of the Contact Type**
MORRIS LEIDER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York

5:00 **Special Demonstration: Identification of Specific Allergen in Bacterial Allergy**
HERMANN BLATT, M.D., Cincinnati, Ohio

SATURDAY, FEBRUARY 10, 1951

Morning Session—West Lounge

9:00-12:00 Nasal Allergy

ETHAN ALLAN BROWN, M.D., Lecturer in Allergy, Tufts College Medical School, Boston, Massachusetts
and Associates:
HAL M. DAVISON, M.D., Atlanta, Georgia
GILES A. KOELSCHE, M.D., Rochester, Minnesota
HOMER E. PRINCE, M.D., Houston, Texas
OLIVER E. VAN ALYEA, M.D., Chicago, Illinois
ROGER P. WODEHOUSE, M.D., Pearl River, New York

Seasonal Hay Fever
Pollinosis
Molds
Other Seasonal Dusts
Perennial Nasal Allergy
(Diagnosis and treatment with the exception of methods of testing)

12:00-2:00 LUNCH

Afternoon Session—West Lounge

BRONCHIAL ASTHMA

2:00-2:30 Pathology

MILTON G. BOHROD, M.D.,* Director of Laboratories, Rochester General Hospital, Rochester, New York

2:30-4:30 Differential Diagnosis

LEON UNGER, M.D., Associate Professor of Medicine, Northwestern University Medical School, Chicago, Illinois, and Associates

Specific Therapy
Non-specific Therapy
Drug Therapy

4:30-5:00 Special Lecture on Status Asthmaticus

HENRY D. OGDEN, M.D., Clinical Assistant Professor of Medicine, Louisiana State University School of Medicine, New Orleans, Louisiana

SUNDAY, FEBRUARY 11, 1951

Morning Session—West Lounge

9:00-10:00 Gastrointestinal Allergy

ORVAL WITHERS, M.D., Associate Professor of Medicine, University of Kansas School of Medicine, Lawrence-Kansas City, Kansas

10:00-11:00 Food Allergy—Clinical Diagnosis and Management

ORVAL WITHERS, M.D., Associate Professor of Medicine, University of Kansas School of Medicine, Lawrence-Kansas City, Kansas

11:00-12:00 Vernal Conjunctivitis and Other Ocular Allergies

M. MURRAY PESHKIN, M.D., New York, New York

12:00-2:00 LUNCH

Afternoon Session—West Lounge

MISCELLANEOUS ALLERGIES

2:00-3:00 Ménière's Disease, Migraine and Other Allergic Headaches

JOHN H. MITCHELL, M.D., Assistant Clinical Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio

3:00-3:40 Cardiovascular System and Periarteritis Nodosa

FRED W. WITTICH, M.D., Minneapolis, Minnesota

3:40-4:00 Urinary Tract

SUSAN C. DEES, M.D., Associate Professor of Pediatrics and Allergy, Duke University School of Medicine, Durham, North Carolina

4:00-5:00 Newer Knowledge in the Therapy of Allergic Diseases (ACTH)

THERON G. RANDOLPH, M.D., Instructor in Medicine, Northwestern University Medical School, Chicago, Illinois

*By invitation

SEVENTH ANNUAL CONGRESS

THE AMERICAN COLLEGE OF ALLERGISTS, INC.

February 11-14, 1951

Edgewater Beach Hotel

Chicago

Ballroom—Edgewater Beach Hotel

Seventh Annual Congress

SUNDAY, FEBRUARY 11, 1951

2:00 p.m. **Registration**—The Foyer

MONDAY, FEBRUARY 12, 1951

Morning Session—The Ballroom

GENERAL SESSION

Chairman: JOHN D. GILLASPIE, M.D., Boulder, Colorado

9:00-9:10 **The Diagnosis and Treatment of Bacterial Allergy**
HERMANN BLATT, M.D., Cincinnati, Ohio

9:20-9:30 **House Dust as a Cause and Carrier of Disease**
ALBERT H. UNGER, M.D., Clinical Assistant, Northwestern University Medical School; Attending Staff, Columbus Hospital, Chicago, Illinois

9:40-9:50 **Comparison of Anamnestic Therapy with Perennial and Preseasonal Therapy in the Treatment of Pollinosis**
LEWIS E. ABRAM, M.D., and JEROME S. FRANKEL, M.D., Cleveland, Ohio

10:00-10:10 **Present Status of the Use of Ergot in Migraine**
LESTER S. BLUMENTHAL, M.D.* Clinical Instructor in Medicine, George Washington University Hospital; Attending Physician, George Washington and Gallinger Municipal Hospitals; Chief of the Headache Clinic, George Washington University Hospital, Washington, D. C.

MARVIN FUCHS, M.D.,* Clinical Instructor in Medicine, George Washington University School of Medicine; Attending Physician, George Washington and Gallinger Municipal Hospitals; Associate in the Allergy and Headache Clinics, George Washington University Hospital, Washington, D. C.

10:20-10:30 **Allergic Aspects of Psychiatry**
THERON G. RANDOLPH, M.D., Instructor in Medicine, Northwestern University Medical School, Chicago, Illinois

* * *

There will be a 10-minute discussion following each paper.

10:30-11:00 **RECESS TO VISIT EXHIBITS**

11:00-11:10 **Studies of the 11-Oxycorticosteroids of Allergic Patients Treated with ACTH (Armour)**

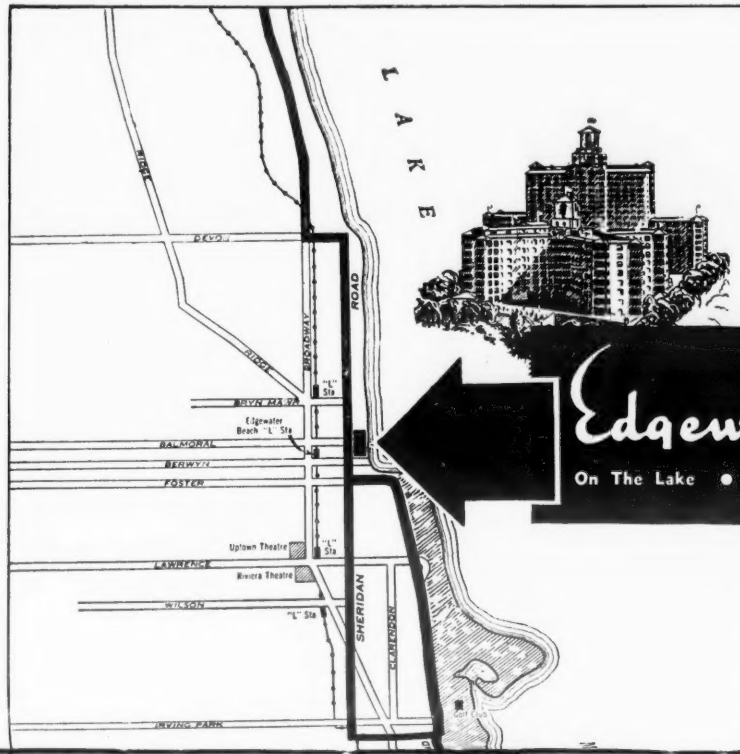
ALLAN J. STANLEY, Ph.D.,* Department of Physiology, University of Oklahoma School of Medicine and University Hospitals
GEORGE S. BOZALIS, M.D., Department of Internal Medicine, University of Oklahoma School of Medicine and University Hospitals, Oklahoma City, Oklahoma
in collaboration with
DICK H. HUFF, M.D., VERNON D. CUSHING, M.D., and LEO CAWLEY, M.D.

11:10-11:20 **ACTH in the Treatment of Hay Fever**
MICHAEL ZELLER, M.D., Clinical Instructor in Medicine, University of Illinois College of Medicine, Chicago, Illinois

11:20-11:30 **Observations on the Use of ACTH and Cortisone in the Treatment of Hay Fever and Asthma**
SIDNEY FRIEDLAENDER, M.D., Instructor in Clinical Medicine, Wayne University College of Medicine, Detroit, Michigan

ALEX S. FRIEDLAENDER, M.D., Instructor in Clinical Medicine, Wayne University College of Medicine, Detroit, Michigan

*By invitation



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*8:15	1:30	8:35	2:00
*8:45	3:00	9:05	3:25
*9:15	3:30	9:35	3:55
10:00	4:10	10:25	4:40
10:30	4:45	10:55	5:15
11:15	5:15	11:45	5:45

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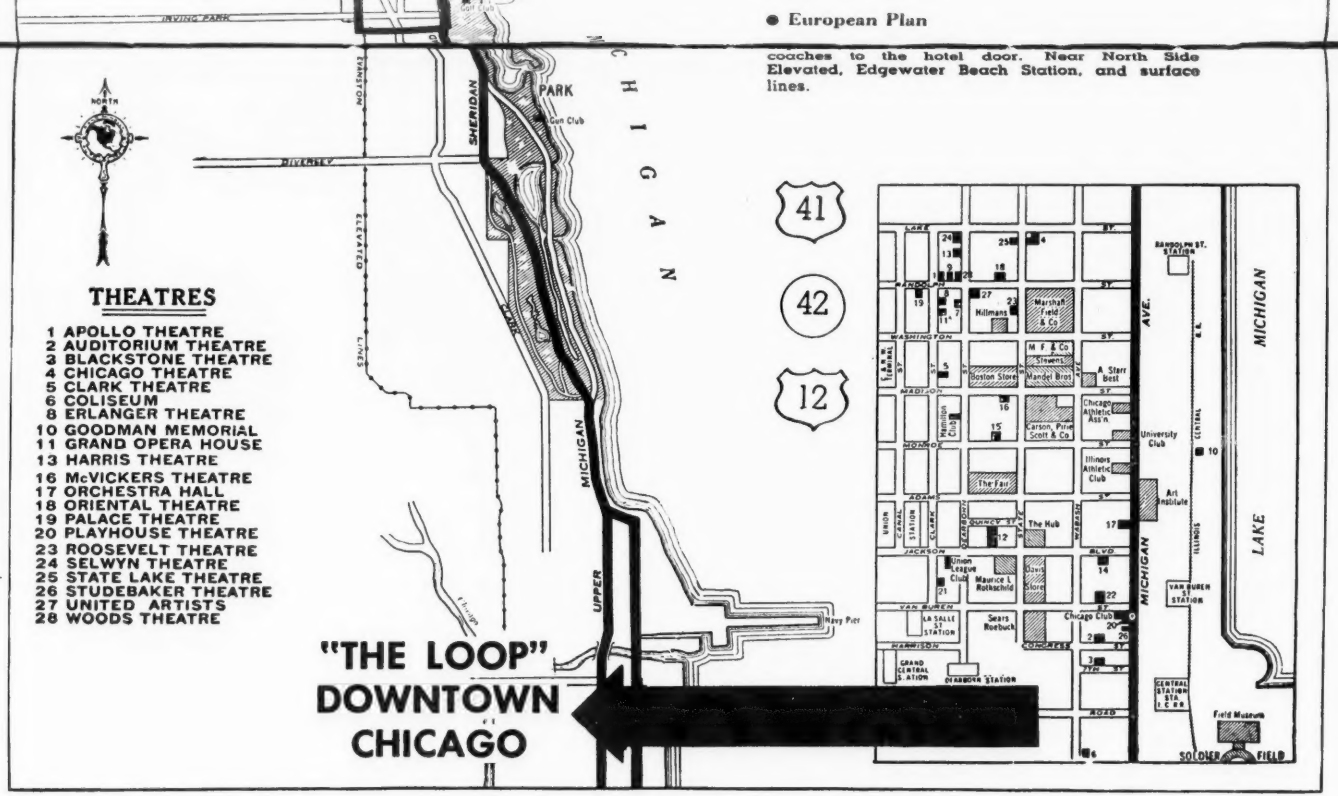


11:30-11:40 **Studies on the Therapeutic Effects of ACTH and Cortisone in Asthma and Other Allergic Conditions**

BRAM ROSE, M.D.,* Associate Professor of Medicine, McGill University, Montreal, Canada

in collaboration with

J. A. P. PARE, M.D., K. K. PUMP, M.D., and R. L. STANFORD, M.D., Montreal, Canada

11:40-11:50 **The Use of ACTH in Ambulatory Patients with Severe Bronchial Asthma**

ETHAN ALLAN BROWN, M.D., Lecturer in Allergy, Tufts College Medical School, Boston, Massachusetts

* * *

Open discussion will be held following the ACTH symposium.

LUNCH

Afternoon Session—The Ballroom

SECTION ON PSYCHOSOMATIC ALLERGY

Chairman: HAROLD A. ABRAMSON, M.D., New York City

2:00-2:15 **Some Psychological Aspects of the Treatment of Patients Who Have Food Allergies**

WILLIAM KAUFMAN, Ph.D., M.D., Bridgeport, Connecticut

2:25-2:40 **An Asthmatic Death in Which Psychic Influences Were an Aggravating Factor. Case Report.**

REDFORD A. WILSON, M.D., Tucson, Arizona

and

JAMES A. SUTTON, M.D., Tucson, Arizona

2:30-3:05 **The Role of the Specialist in Psychotherapy**

FRANK FREMONT-SMITH, M.D.,* Medical Director, The Josiah Macy, Jr., Foundation, New York, New York

3:15-3:45 **RECESS TO VISIT EXHIBITS**

3:45-4:00 **The Genesis and Treatment of a Recurrent Attack of Asthma**

HYMAN MILLER, M.D., Beverly Hills, California

and

DOROTHY BARUCH, Ph.D.,* Beverly Hills, California

4:10-4:25 **Psychotherapy in Multiple Sclerosis**

HINTON D. JONEZ, M.D., Medical Director, Multiple Sclerosis Clinic, St. Joseph's Hospital, Tacoma, Washington

4:35-4:50 **Technic for Screening Verbatim Psychotherapeutic Recordings and Its Application to Allergic Patients**

HAROLD A. ABRAMSON, M.D., Chief, Allergy Clinic, Mt. Sinai Hospital, New York, New York

5:00-5:15 **Combined Allergic and Psychosomatic Treatment in Bronchial Asthma**

ETHAN ALLAN BROWN, M.D., Lecturer in Allergy, Tufts College Medical School, Boston, Massachusetts

* * *

There will be a 10-minute discussion following each paper.

*By invitation

Evening—West Lounge

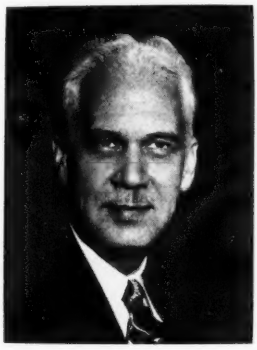
6:00 Cocktail Party
Courtesy of the SCHERING CORPORATION, Bloomfield, New Jersey

7:00 Color Movies: Light Plane Caravan to Guatemala
HERMAN HEISE, M.D., Milwaukee, Wisconsin

TUESDAY, FEBRUARY 13, 1951

Morning Session—The Ballroom

9:00 Presidential Address
JOHN H. MITCHELL, M.D., Assistant Clinical Professor of Medicine, Ohio State University College of Medicine, Columbus, Ohio



ARILD E. HANSEN

9:20 Dietary Fat in Relation to Integrity of Skin
Guest Speaker
ARILD E. HANSEN, M.D., Chairman, Department of Pediatrics, School of Medicine, University of Texas, Galveston, Texas

10:00 Recess

10:15 Business Meeting

12:30 Dinner-Luncheon in the Marine Dining Room

Afternoon Session—The Ballroom

SECTION ON PEDIATRICS

Chairman: BERT RATNER, M.D., New York City

2:00-2:15 Milk Allergy in Infants
NORMAN W. CLEIN, M.D., Children's Clinic; Clinical Assistant Professor of Pediatrics, University of Washington School of Medicine, Seattle, Washington

2:25-2:40 Experiences with ACTH in the Treatment of Asthma and Eczema in Infancy and Childhood*
JEROME GLASER, M.D., Assistant Professor of Pediatrics, University of Rochester School of Medicine and Dentistry; Pediatrician-in-Chief, Genesee Hospital, Rochester, New York

2:50-3:05 Management of Asthma in Infancy
STANLEY S. FREEDMAN, M.D., Providence, Rhode Island

*Authors of paper: JEROME GLASER, M.D.; SHELDON C. SIEGEL, M.D.; JACOB D. GOLDSTEIN, M.D.; and RICHARD S. MELTZER, M.D., Rochester, New York.

3:15-3:45 RECESS TO VISIT EXHIBITS

3:45-4:00 Allergic Epilepsy

SUSAN C. DEES, M.D., Associate Professor of Pediatrics and Allergy, Duke University School of Medicine, Durham, North Carolina
and
HANS LOWENBACH, M.D.,* Associate Professor of Neuropsychiatry, Duke University School of Medicine, Durham, North Carolina

4:10-4:25 The Present Status of Pediatric Allergy

BRET RATNER, M.D., Professor of Clinical Pediatrics, New York Medical College, New York, New York

4:35-4:50 Antihistaminic Poisoning in Children

HAROLD I. LECKS, M.D.,* Assistant Allergist, Children's Hospital, Philadelphia, Pennsylvania; Instructor in Pediatrics, University of Pennsylvania Medical School, Philadelphia, Pennsylvania

5:00-5:10 Repository Penicillin Injections in Allergic Children

SAMUEL J. LEVIN, M.D., Detroit, Michigan

5:20-5:35 Ragweed Pollinosis—a Public Health Problem in School Children

SHELDON C. SIEGEL, M.D.,* Instructor in Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York

5:35-5:45 Skeletal Abnormalities Commonly Associated with Allergic Disorders

NORMAN A. POKORNY, M.D., Springfield, Massachusetts

* * *

There will be a 10-minute discussion following each paper.

Evening Session—Michigan Room

COMMITTEE ON DERMATOLOGIC ALLERGY

Chairman: STEPHAN EPSTEIN, M.D., Marshfield, Wisconsin

DERMATOLOGY ROUND TABLE

Moderator: RUDOLF L. BAER, M.D.,† New York City

7:30 P.M.

Participants:

HERBERT RATTNER, M.D.,* Associate Professor of Dermatology, Northwestern University Medical School, Chicago, Illinois

STEPHEN ROTHMAN, M.D.,* Professor of Dermatology, University of Chicago, Chicago, Illinois

JAMES R. WEBSTER, M.D.,* Professor of Dermatology, Northwestern University Medical School, Chicago, Illinois

MORRIS LEIDER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York

ADOLPH B. LOVEMAN, M.D., Assistant Clinical Professor of Dermatology and Syphilology, University of Louisville School of Medicine, Louisville, Kentucky

STEPHAN EPSTEIN, M.D., Marshfield Clinic, Marshfield, Wisconsin; Clinical Associate Professor of Dermatology, University of Minnesota Medical School, Minneapolis, Minnesota

ADOLPH ROSTENBERG, JR., M.D., Assistant Professor of Dermatology and Associate Director of the Allergy Unit, Illinois College of Medicine, Chicago, Illinois

NOTE: This is a question and answer round table. Please submit questions at least one day in advance at the Registration Desk, marking questions for the attention of Moderator Rudolf L. Baer, M.D.

Following the round table, there will be an informal gathering of those members of the College who are interested in dermatology, for the purpose of starting a permanent Dermatologic Group within the College.

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*By invitation

†RUDOLF L. BAER, M.D., Associate Professor of Clinical Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York.

WEDNESDAY, FEBRUARY 14, 1951

Morning Session—The Ballroom

SECTION ON OTOLARYNGOLOGY

Chairman: GEORGE E. SHAMBAUGH, JR., M.D., Chicago, Illinois

9:00-10:15 SYMPOSIUM

Sinus Versus Allergic Headache

GEORGE E. SHAMBAUGH, JR., M.D., Associate Professor of Otolaryngology, Northwestern University Medical School, Chicago, Illinois

Histamine and Headache

FRENCH K. HANSEL, M.D., Director, Hansel Foundation; Associate Professor Clinical Otolaryngology-Laryngology, Washington University School of Medicine, St. Louis, Missouri

Ocular Headache

ALBERT D. RUEDEMANN, M.D.,* Professor of Ophthalmology, Wayne University College of Medicine, Detroit, Michigan

10:15-10:45 RECESS TO VISIT EXHIBITS

SECTION ON DERMATOLOGY

Chairmen: MORRIS LEIDER, M.D.,† and RUDOLF L. BAER, M.D.,‡ New York City

10:45-11:00 Periorbital Dermatitis

BOEN SWINNY, M.D., San Antonio, Texas

11:10-11:20 Urticaria Due to Pollen

GEORGE L. WALDBOTT, M.D., Detroit, Michigan
in collaboration with
KARL MERKLE, M.D.,* Detroit, Michigan

11:30-11:40 Sensitivity Patterns in Ragweed Dermatitis

S. M. MACKOFF, M.D.,* Department of Dermatology, University of Minnesota, Minneapolis, Minnesota
in collaboration with
A. ORVILLE DAHL, M.D.,* Professor of Botany, University of Minnesota, Minneapolis, Minnesota

11:50-12:00 Infantile Eczema in a Rural District—A Ten-year Study

STEPHAN EPSTEIN, M.D., Marshfield Clinic, Marshfield, Wisconsin; Clinical Associate Professor of Dermatology, University of Minnesota Medical School, Minneapolis, Minnesota
with the assistance of
MARIE PALECEK, R.N.

* * *

There will be a 10-minute discussion following each paper.

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*By invitation

†MORRIS LEIDER, M.D., Assistant Clinical Professor of Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York.

‡RUDOLF L. BAER, M.D., Associate Professor of Clinical Dermatology and Syphilology, New York University Postgraduate Medical School, New York, New York.

LUNCH

Afternoon Session—The Ballroom

PANEL: RHEUMATISM AND ARTHRITIS

Chairman: GEORGE E. ROCKWELL, M.D., Milford, Ohio

2:00-2:10 The Over-all Picture of Rheumatism and Arthritis

WILLIAM KAUFMAN, Ph.D., M.D., Bridgeport, Connecticut

2:10-2:30 Pathology of Rheumatism and Arthritis

M. G. BOHROD, M.D.,* Director of Laboratories, Rochester General Hospital, Rochester, New York

2:30-2:40 Food Allergy as a Factor in Rheumatoid Arthritis

MICHAEL ZELLER, M.D., Clinical Instructor in Medicine, University of Illinois College of Medicine, Chicago, Illinois

2:40-3:10 Physiologic, Metabolic, and Toxic Effects of ACTH and Cortisone

THOMAS F. DOUGHERTY, Ph.D.,* Professor and Chairman, Department of Anatomy, University of Utah School of Medicine, Salt Lake City, Utah

3:10-3:40 RECESS TO VISIT EXHIBITS

3:40-3:55 Clinical Use of ACTH and Cortisone

THERON G. RANDOLPH, M.D., Instructor in Medicine, Northwestern University Medical School, Chicago, Illinois

3:55-4:05 Chemical Agents Which May Be Used in Therapy as Substitutes for ACTH and/or Cortisone

C. R. K. JOHNSTON, M.D., Head of Department of Allergy, Cleveland Clinic, Cleveland, Ohio

* * *

The Panel will be followed by a round table discussion.

*By invitation

IF TIME PERMITS

The Acid-Anoxia-Endocrine Theory of Allergy

HARRY G. CLARK, M.D.,* and THERON G. RANDOLPH, M.D., Chicago, Illinois

The Clinical Evaluation of Ambodryl Hydrochloride

J. WARRICK THOMAS, M.D., and FRANK R. KELLY, JR., M.D.,* Richmond, Virginia

Standardization of Pollen Extracts by Precipitin

ROGER P. WODEHOUSE, M.D., Pearl River, New York

TO BE READ BY TITLE

Treatment of Certain Dermatoses as Bacterial Allergies

K. A. BAIRD, M.D., West Saint John, New Brunswick, Canada

Natural Steroid Complex in the Treatment of Bronchial Asthma

S. H. JAROS, M.D., and AARON D. SPIELMAN, M.D., New York, New York

Survey of Air-borne Fungus Spores of the Boston Area in Relation to Inhalant Allergies

LEO KAPLAN, Ph.D.,* Carbondale, Illinois

The Treatment of Certain Allergic Syndromes with Parenteral Diphenhydramine Hydrochloride

WILLIAM H. LIPMAN, M.D., Kenosha, Wisconsin

The Single Injection Treatment of Hay Fever. Study IV

A. L. MAIETTA, M.D., Boston, Massachusetts

Mold Fungi in the Etiology of Respiratory Allergic Diseases. XV. Further Survey Studies

MARIE BETZNER MORROW, Ph.D., Austin, Texas

A New Method and Medium for Administering and Controlling the Action of Therapeutic Agents with Particular Reference to Epinephrin

ROY A. OUER, M.D., San Diego, California

Newer Drugs and Their Use in Allergy

JOSEPH H. SHAFFER, M.D.,* Detroit, Michigan

The Gothlin Index in Allergic Disease

HYMAN SHERMAN, M.D., Brooklyn, New York; JEROME SHERMAN, M.D.,* Baltimore, Maryland; THEODORE D. COHN, M.D.,* Brooklyn, New York

*By invitation

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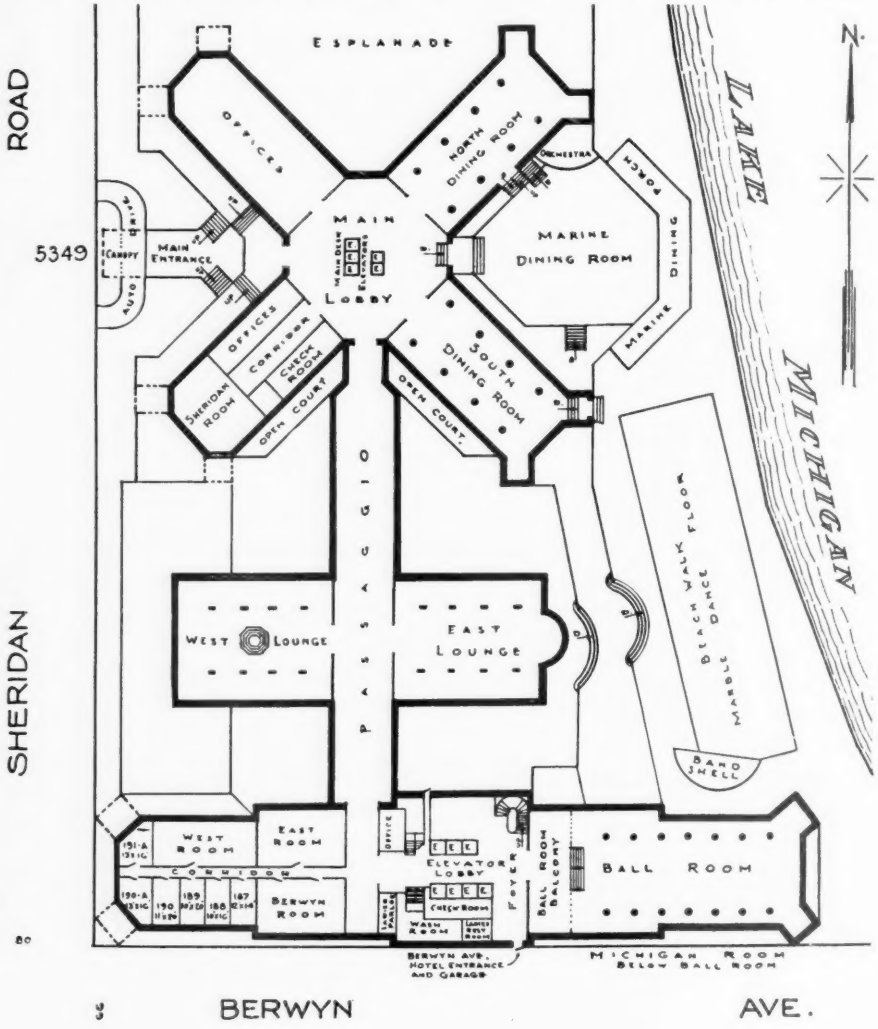

THE USE OF DIBENAMINE IN THE SEVERE ASTHMATIC STATE AND RELATED CHRONIC PULMONARY CONDITIONS

S. D. KLOTZ, M.D., and CLARENCE BERNSTEIN, M.D., F.A.C.A., F.A.A.A.
Orlando, Florida

ALTHOUGH the therapy for severe asthmatic states has improved markedly in recent years with the advent of epinephrine and related sympathomimetic drugs, aminophylline and similar derivatives, antibiotics, aerosol mechanisms, et cetera, there are frequent instances when additional therapeutic help is most urgently needed.

Recently several groups of "adrenergic blocking agents" have been synthesized which specifically inhibit certain responses of effector cells to epinephrine, to related amines, and to sympathetic nerve impulses. One such group belongs to the B-haloalkylamine series, of which Dibenamine (N,N-Dibenzyl-B-chlorethylamine) Chloride may be considered as the prototype. At the present time, the blockade produced by members of this group of compounds appears to be more complete and specific than that produced by members of other series.

The most prominent action of Dibenamine is a specific blockade of certain excitatory responses to epinephrine and sympathetic nerve activity. Pressor responses to exogenous and endogenous epinephrine are blocked and reversed in most animals. Dibenamine provides marked protection against lethal effects of epinephrine. Depression of the central nervous system does not appear to be a significant factor in the inhibition of vasomotor reflexes, for it appears to be adequately established that the drug is devoid of actions on the autonomic ganglia and on reflex pathways in the central nervous system. Dibenamine does not block or reverse the inhibitory sympathetic functions. Smooth muscles which are relaxed by epinephrine or sympathetic stimulation are uninfluenced.

It is of both theoretical and practical interest that certain Dibenamine derivatives produce not only adrenergic blockade but are also antagonistic to histamine, as shown by Loew and Nickerson and their respective coworkers.[5,7] Some of the compounds examined are many times more potent in animals than are the antihistaminic drugs currently employed in therapeutics. They are also characterized by remarkably long duration of antihistaminic action. Speculation as to the chemical basis and pharmacological import of the concomitance of anti-adrenergic and antihistaminic actions must be clarified by further investigations.

In the over-all picture of the severe asthmatic state, with its anoxia and accompanying pulmonary arterial hypertension, pallor, sweating, rapid thready pulse, marked anxiety, and finally terminal exhaustion with shock-like syndrome, it appeared to us that certain of these features were

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not only not useful but were even harmful. If a drug with the properties of Dibenamine could block the noxious "pressor" effects of endogenous epinephrine and exogenous epinephrine derivatives without at the same time losing the desired inhibitory action on the smooth muscle of the bronchial tree, such a drug would be a valuable adjunct in potentiating the action of adrenaline in severe asthma, particularly in so-called "adrenaline-fast" states.

METHOD AND RESULTS

Dibenamine was administered to twenty patients with severe bronchial asthma. Six of these were in status asthmaticus and had become resistant to epinephrine, to related sympathomimetic drugs, and to the other usual therapeutic agents. Four patients had a chronic pulmonary pathologic condition with an associated cor pulmonale, anoxia, and bronchospastic features. All had been under treatment for two or more days with the customary therapy with little relief or with actual deterioration in their condition. After the second day of controlled observation, Dibenamine was additionally administered.

Dibenamine* can be given either orally or intravenously. For the oral route, it was supplied in the form of coated tablets, each containing 130 mg (2 grains). Dosage varied from one or two tablets every three to four hours. For intravenous medication a sterile 5 per cent solution in alcohol—propylene glycol, each cubic centimeter containing 50 mg of Dibenamine—was diluted into a 300 to 500 cc unit of normal saline, or 5 per cent glucose, infusion. Dosage was calculated at 5 to 7 mg per kg of body weight, with rate of flow adjusted so that the intravenous infusion required not less than sixty minutes. Since Dibenamine and other B-haloalkyl groupings are related to the nitrogen mustard series, there is local tissue damage if given via subcutaneous, intramuscular or intraperitoneal routes. There is some local irritation with oral administration, and in some instances this interferes greatly in its therapeutic effect.

In all cases except two, the oral route was employed. Practically *every* patient (in whom therapeutic levels of the drug could be attained) experienced subjective relief within eight to fourteen hours. There was a marked decrease in anxiety, dyspnea, and tightness of the chest. The pale and anxious patient with cold perspiration and thready peripheral pulse was gradually and occasionally rapidly returned to a normal status. Pulsus paradoxicus, frequently seen in many of the severe asthmatics, quickly improved or disappeared altogether. There was marked amelioration in the patients' vital capacity along with clearing of the typical auscultatory findings in the chest. Usually within forty-eight hours the patients were comfortable, whereas previously some had been in almost continuous severe distress for two or three weeks. Most of the patients' systemic blood pressure readings were low to normal with little change following

*Material furnished for investigational uses by Smith, Kline & French Company.

Dibenamine. No major complications caused by the drug were noted. Some of the patients had vague mental excitation which resembled in some respects that seen in procaine excitement. The most frequent adverse side reaction was nausea with or without vomiting, which, unless too severe, did not detract from the clinical effectiveness of the drug but thereby possibly added an adjuvant expectorant action. In several patients, because of vomiting, adequate dosage levels could not be attained or the drug had to be discontinued. At present we are trying to solve this problem by the use of gastric anesthetic-sedative agents and demulcents, or by combination with procaine. In many of our chronic but less severe cases, we have overcome the nausea by starting with a small oral dose and gradually increasing to tolerance. One of the most acutely ill patients came under our care with severe vomiting caused by an injection of morphine to which she had an idiosyncrasy. Following Dibenamine intravenously, her nausea and vomiting persisted for another thirty-six hours. That Dibenamine contributed to its persistence is a strong probability.

DISCUSSION

Many clinicians agree in the belief that there is an altered reaction to epinephrine in many of the patients with bronchial asthma. H. Abramson in his discussion of the psychosomatic aspects of asthma states that an undercurrent of anxiety exists in all of these cases and feels that many of such patients tolerate sympathomimetic drugs poorly. Cameron[1] feels that through long stress the individual's tendency to develop tension has become so augmented—both with regard to the ease with which the reaction is elicited and with regard to its intensity—as to make the small hour-to-hour stress of daily living, formerly barely noticed, sufficient in the now over-reactive individual to perpetuate his symptoms. His anxiety states have now become self-sustaining. Subsequent dealing with primary causes can no longer remove completely the autonomous sequences. Cameron tried to interrupt such sequences by decreasing the general reactivity of the individual by means of desensitizing doses of epinephrine.

Curry et al[2] study the effect of another adrenergic blocking agent, Dihydroergocornine, on pulmonary responses to histamine and methacholine in subjects with bronchial asthma. Previous reports had shown that interruption of the sympathetic nervous system in the lung brings about cessation of asthmatic attacks in certain individuals, as with procaine block of the sympathetic pathways. Their results indicated that in some cases the sympatholytic agent furnished remarkable protection against the pulmonary reaction to histamine and methacholine.

Motley[6] has shown that anoxia causes pulmonary vasoconstriction. There is a rise of pulmonary artery pressure due to stasis of the smaller pulmonary vessels and pulmonary arterioconstriction. Zimmerman[10] has measured the pulmonary artery pressure in human beings in severe asthma and found the pressure elevated in all cases.

Koenig and Koenig[4] in a recent study of pulmonary edema produced in animals by toxic doses of ammonium salts found that this pulmonary edema could be prevented by low cervical and high thoracic spinal cord transections, by the "alarm reaction," and by Dibenamine. This was felt to be strong evidence for the importance of sympathetic impulses in this phenomenon. Blocking parasympathetic nerve impulses was ineffectual in preventing this edema. Recent experiments[8] in dogs have now demonstrated that adrenergic blockade with Dibenamine provides marked protection against both hemorrhagic and traumatic shock. This protection is largely due to the elimination of reflex vasoconstriction which ordinarily sustains blood pressure at the expense of blood flow. Recent work suggests that there are adrenergic and cholinergic agents secreted by the hypothalamus, neurohypophysis and proximal portions of the adenohypophysis, whence they are carried via the hypophyseal portal circulation to the pars distalis of the adenohypophysis.[3] While it has not been shown that adrenergic blocking agents inhibit responses of the central nervous system to adrenergic stimuli, yet the probable value of the elimination of excessive adrenergic stimuli to the brain centers has not to our knowledge been thoroughly investigated. Rockwell,[9] however, has reported benefit from Dibenamine in certain psychopathologic syndromes associated with markedly increased anxiety and abnormal blood levels of adrenaline.

No ideal blocking adrenergic agent is as yet available, but compounds with improved specificity and potency are rapidly being developed. At present, Dibenamine appears to be the most effective drug available. Its value in severe bronchial asthma and chronic pulmonary diseases with anoxia first suggested itself on the theoretical possibility that it might correct certain of the pathologic-physiologic alterations produced within the body by these states. In a majority of instances, the clinical result confirmed our most enthusiastic expectations; in some, less striking alterations were noted. We present our findings at this time with the hope that other allergy researchers may become interested in this new therapeutic adjunct which may prove very useful in a most difficult clinical entity.

SUMMARY

1. Dibenamine, a new adrenergic blocking agent, was used as a therapeutic adjunct in cases of severe bronchial asthma and chronic pulmonary diseases with anoxia with some excellent results.

2. Dibenamine is felt to be of value in these states by virtue of its sympathoadrenalytic effect which reverses the vasopressor responses to epinephrine but does not alter its inhibitory effect on the bronchial musculature. In this manner the increased pulmonary arterial tension and congestion that develop are decreased, and consequently both the pulmonic and systemic circulations are improved.

3. Dibenamine appears also to increase markedly the body tolerance for sympathomimetic substances as well as the sensitivity to their inhibitory effects, a property that may be of particular help in so-called "adrenaline-fast" states.

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740 Magnolia Avenue

SEVERE SERUM-SICKNESS TYPE OF PENICILLIN REACTION

(Continued from Page 753)

5. Because of its ability to sensitize penicillin should not be used indiscriminately. Its use should be reserved for those cases when the physician feels that not to do so would be jeopardizing the health of his patient.

6. A severe case of delayed serum sickness following penicillin, which did not yield to any of the known antihistaminic drugs, has been reported together with a brief review of the literature of similar cases.

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741 Madison Avenue

PREGNANCY AND THE TREATMENT OF HAY FEVER, ALLERGIC RHINITIS, AND POLLEN ASTHMA

SAUL W. CHESTER, M.D., F.A.C.A.

Paterson, New Jersey

THE LITERATURE on the treatment of allergies that existed or appear during pregnancy is indeed meager. Ratner[1] states that it is the general consensus that females do not lose their sensitivities during gestation. Urbach[2] states that the assumed presence of antibodies in the pregnant woman serves to explain the good results achieved with systemic injections of the serum of pregnant women in the treatment of the dermatoses of pregnancy. Waldbott and Bailey[3] demonstrated improvement in some menstrual asthmas with estrogenic therapy. No mention is made of the treatment of pollenosis, vasomotor rhinitis, or pollen asthma complicated by pregnancy. Since 1935 I have been treating pregnant women suffering from pollenosis, vasomotor rhinitis, and pollen asthma with consistently good average results. At no time were constitutional reactions obtained, and all were delivered in the usual manner with no fatalities. In all, twenty cases are presented: nine primipara and eleven multipara.

TABLE I

Name Age	Prima-para	Multi-para	History	Diagnosis	Date treatment started	Perennial	Date of delivery	Complications
Mrs. R.M. 26 years	X		Pollen asthma 1 year	Ragwood hay fever and chronic urticaria	1/5/35	X	12/5/36	None
Mrs. S.Y. 24 years		2 3 4 5	Pollenosis and pollen asthma 4 years	Pollenosis and pollen asthma	1/2/34	X	10/31/36 8/18/39 2/ 3/43 7/19/45	None None None None
Mrs. T.D. 32 years		2	Hay fever and asthma 10 years	Pollenosis (ragweed) and pollen asthma	1/2/36	X	2/1/37	None
Mrs. S.R. 22 years	X		Hay fever 5 years	Pollenosis (grass and ragweed)	2/3/36	X	3/18/37	None
Mrs. A.O'S. 23 years	X		Hay fever 4 years	Pollenosis (ragweed)	2/10/40	X	3/5/41	None
Mrs. O.Y. 29 years		2	Hay fever 3 years	Pollenosis (ragweed) and dust sensitivity	5/8/43	X	11/22/43	None
Mrs. A.I. 22 years	X		Hay fever and asthma 5 years	Pollenosis (grass and ragweed), pollen asthma	1/3/40	X	2/1/43	None
Mrs. G.C. 26 years	X		Hay fever 2 years	Pollenosis (grass and ragweed)	10/20/45	X	11/28/47	None
Mrs. F.M. 31 years		6	Hay fever and asthma 7 years	Ragweed pollen asthma, vasomotor rhinitis	10/30/45	X	8/31/46	None

TABLE I (continued)

Name Age	Prima-para	Multi-para	History	Diagnosis	Date treatment started	Perennial	Date of delivery	Complications
Mrs. C.R. 25 years		1	Hay fever 9 years	Pollenosis (grass and dust)	1/25/47	X	7/17/47 at birth; no trea	Lost first child received tment at that time
Mrs. L.B. 28 years		2	Hay fever 10 years	Pollenosis (grass and ragweed), dust sensitivity	4/26/44	X	7/12/48	None
Mrs. D.C. 40 years		2	Asthma and vasomotor rhinitis 4 years	Asthma and vasomotor rhinitis	7/12/48	X	1/6/49	None
Mrs. C.D. 26 years		3	Hay fever and asthma 10 years	Pollenosis and pollen asthma	10/7/48	X	7/15/49	None
Mrs. M.O. 26 years	X		Grass hay fever and vasomotor rhinitis	Pollenosis and vasomotor rhinitis	8/5/48	X	2/6/49	None
Mrs. I.G. 24 years		1	Hay fever 4 years	Pollenosis (grass and ragweed)	1/2/46	X	2/15/49	None
Mrs. F.J.M. 25 years	X		Hay fever 1 year Hives 3 years	Pollenosis (grass and ragweed), chronic urticaria	2/16/44	X	6/2/49	None
Mrs. O.D. 25 years		2	Erythema, pruritis, vasomotor rhinitis 3 years	Pruritus, vasomotor rhinitis	2/3/47	X	6/2/48	Lost first child at term; no treatment
Mrs. J.L.D. 29 years		2	Spring and fall hay fever 3 years Eczema at age 14; left her at 16	Pollenosis (grass and ragweed)	2/7/44	X	11/12/46	None
Mrs. M.L.	X		Hay fever 4 years	Pollenosis (grass and ragweed)	2/3/42	X	7/25/49	None
Mrs. J.S.K. 21 years		2	Spring and fall hay fever 4 years	Pollenosis (grass and and ragweed)	2/3/48	X	9/3/49	None

CONCLUSION

This report is based on personal experience gathered over a period of fifteen years, presented in the hope that it will act as a guide in the treatment of allergies arising or pre-existing in the pregnant woman. Each patient must be tested thoroughly, evaluated properly from the clinical history, and treated, not with heroic doses but cautiously and wisely. The pregnant woman tolerates moderate doses well, and the pregnancy usually terminates happily. Specific pollen therapy is the method of choice, starting with preseasonal treatment given in gradually increasing doses, reaching a maximum before the season starts, continuing through the season at proper intervals (once weekly) and leading into the perennial

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KAPOSI'S VARICELLIFORM ERUPTION TREATED WITH AUREOMYCIN

CHARLES HYMAN, M.D., F.A.C.A.
Atlantic City, New Jersey

KAPOSI'S varicelliform eruption has had considerable notice in the literature. Many reports are available as to its incidence, its relative occurrence in infants and adults, and its etiological nature. The viral nature of the disease has been demonstrated by many observers. Hershey and Smith[7] demonstrated vaccinia virus in these lesions. Lynch and Steves[9] reported on the role of the virus of herpes simplex in producing the Kaposi syndrome. Other workers [8,4,11] have demonstrated the same etiological agents. All reports stress the intractability of the disease, two to four weeks being the normal course in favorable cases. Barton and Brunsting[2] reported seventeen deaths among sixty-seven cases, with gangrene a frequent complication.

Finland[6] et al reported success in the treatment of herpes zoster with Aureomycin. Baer and Miller,[1] Bereston and Carliner,[3] and more recently Bookman[5] have also reported similar success in the treatment of Kaposi's varicelliform eruption with Aureomycin. The following case is reported because of the dramatic response to this therapeutic agent.

CASE REPORT

S. H., a twenty-six-year-old white man, was first seen January 21, 1950, because of fever, generalized aching, and a mild coryza. Physical examination was negative except for the coryza, a temperature of 101.2°, and evidence of a longstanding neurodermatitis involving the entire head and neck, and to a lesser degree the arms, trunk and legs. Both eyes presented cataracts attributed to the extensive skin lesion.

The presenting illness was considered as an attack of grippe, and symptomatic therapy with coal tar products was instituted. The following day the temperature gradually rose to 103, and a few vesicles appeared on the upper lip and face. Three hundred thousand units of penicillin was given, and the next day the temperature dropped to 99°. Despite the decrease in the fever, rapid progression of the vesicular lesion took place, and in another twenty-four hours the ears, nose, face, lips, and upper chest (to near the nipple area) were covered with weeping serous lesions. These varied from pin point to pin head in size and became intensely irritating. The entire face, ears, neck, and nose were swollen. The patient complained of pain over the entire head and neck. Speech was extremely difficult, and all motions of the head were painful. The parotid, submaxillary, and cervical lymph glands were enlarged, tender, and painful. When the temperature rose to 104°, an additional 300,000 units of penicillin was administered. Throughout the following two days, January 24 and 25, the temperature remained at 103°. The eruption became more extensive although confined to the same areas. Both eyes were closed by edema of the lids. The conjunctivae were congested. Fifty thousand units of penicillin was given every three hours on January 25 for a twenty-four hour period, with no effect on either the lesion or the fever. A blood count on January 26 showed: hemoglobin 13.5 gm (84 per cent), red blood cells 4,790,000, mean corpuscular

From the Department of Medicine, Atlantic City Hospital, Atlantic City, New Jersey.

hemoglobin 28, white blood cells 6,200, polymorphonuclear cells 69 (nonfilamented 35, filamented 34), lymphocytes 29, monocytes 2. Urine examination was negative. Blood culture was also negative.

At this point a diagnosis of Kaposi's varicelliform eruption was made on the

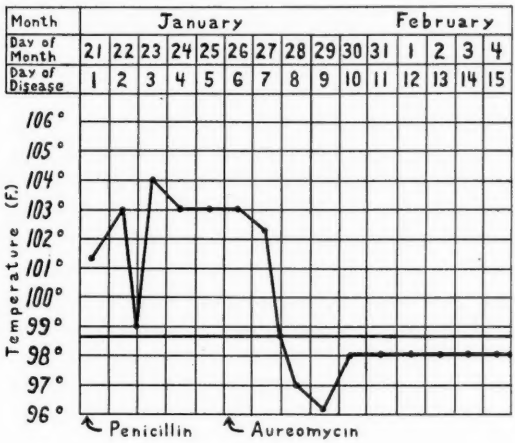

Fig. 1. Temperature chart.

basis of the probable viral nature of the initial febrile illness and the fact that the primary site of the acute skin lesion was a herpetic lesion below the alae nasi. The entire vesicular eruption seemed to extend from this focus. Since active penicillin therapy had failed and at this time it had become obvious that the lesion was of viral origin, a course of Aureomycin therapy was given according to the following schedule: 250 mg at 5 p.m., 6 p.m., 7 p.m., 8 p.m., then every six hours for six doses. Within less than twelve hours the temperature returned to normal and remained at a subnormal level until the patient became ambulant. The vesicles then began to dry and fall off. The generalized skin erythema gradually subsided. All the lymph glands returned to their normal size. Clearing of the lesions was aided by the application of warm boric acid compresses continuously. Numerous areas of skin came away leaving a raw bleeding surface, which healed readily after several days.

The clinical picture in the above case fulfilled the diagnostic criteria for Kaposi's varicelliform eruption.[10] From the history it could be postulated that the point of entrance for the virus was on the upper lip, from secretions produced by the coryza. The initial lesion may have been herpetic. The usefulness of Aureomycin in virus diseases and its recent encouraging results in herpes zoster[6] suggested a trial in this case.

Since this case was treated, a report has appeared by Bookman[5] describing a similar dramatic response in a case of Kaposi's varicelliform eruption. He also notes a second case similarly treated with the same result. Bookman also refers to case reports by Baer and Miller,[1] and Bereston and Carliner,[3] who have treated Kaposi's varicelliform eruption with Aureomycin.

SUMMARY

1. A case of Kaposi's varicelliform eruption is described.

2. Rapid disappearance of the skin lesions took place with Aureomycin therapy.

3. On the basis of this report and similar cases in the literature, further trial with this antibiotic is indicated.

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2807 Pacific Avenue.

NETHAPRIN IN THE TREATMENT OF RESPIRATORY ALLERGY

(Continued from Page 746)

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634 N. Grand Blvd. (3)

ACUTE ALLERGIC CONDITIONS OF THE ABDOMEN
A Clinical Report

F. B. SCHUTZBANK, M.D., F.A.C.A.
Tucson, Arizona

THE physician's ingenuity is often taxed in differentiating between an acute surgical and an acute medical condition of the abdomen. The diagnosis may be made easier in some cases if it is kept in mind that an acute attack of the digestive tract may be the manifestation of a food allergy. Such attacks may simulate a perforated ulcer, gall bladder or renal colic, intestinal obstruction, acute pancreatitis, appendicitis, and coronary or mesenteric thrombosis. For such acute allergic attacks I have used the term "acute allergic conditions of the abdomen." No doubt many emergencies which require surgery, and in which no pathological lesion is found, represent this condition. The writer has never seen a patient with an acute allergic condition of the digestive tract who has not suffered from other definitely allergic conditions, such as seasonal or perennial hay fever, asthma, urticaria, eczema, migraine, or colitis.

All of us have seen cases of chronic dyspepsia, hyperactivity of the bowel with excessive rumbling and gurgling, excessive gas formation, intermittent diarrhea or constipation, so-called nervous stomach and bowels, gastric neuroses, and colitis, that are often, in my opinion, mild food allergy cases. I am certain that many people suffer a long time with chronic digestive tract symptoms, frequently seeking medical aid, when all that would be necessary for relief would be the elimination of some allergenic food to which they are sensitive.

Occasionally, a hypersensitive individual unknowingly ingests an offending food or a larger than normal portion of an allergenic food, and a severe reaction occurs which is responsible for an acute attack of the digestive tract. The following case reports are illustrative:

Case 1.—An engineer, aged thirty-nine, over a period of years suffered acute attacks of excruciating upper abdominal pain associated with collapse, a state of shock and unconsciousness. He was hospitalized in various cities where at least a half a dozen examinations, including x-rays and electrocardiograms, were repeatedly negative. Diagnoses upon admission to a hospital varied from gall bladder and renal colic, perforated ulcer, acute pancreatitis, and coronary or mesenteric thrombosis. Usually, before a diagnosis was agreed upon, the patient recovered, and fortunately, surgery had never been done. Several times on discharge, he was told that he had no doubt passed a gall or kidney stone. Recovery always occurred in two or three days. During an observed attack he was in a state of shock and the liver was palpable and tender. Pain under the right ribs was excruciating. On the third day, there was a subicteric tinge of the sclerae although he was recovering rapidly.

On questioning the patient and his wife, it was learned that he had perennial and seasonal hay fever, chronic dyspepsia with much rumbling and gas in his bowels,

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pruritus ani and a long family history of allergy. After he had recovered he had another examination, including complete allergy testing. In addition to reaction to several pollens and other inhalants, he gave a 4-plus reaction to eggs and chocolate. It then became known that both the last two attacks occurred on a Monday morning about forty-five to sixty minutes after he had eaten four eggs for breakfast. On the preceding days, he had spent the Sundays in the country and had brought home fresh eggs. He said, "They were so good I ate four." Since eliminating eggs and chocolate from his diet, he has had no further acute attacks in several years and his dyspepsia has improved. The pruritus ani and perennial rhinitis cleared up completely. Ingestion of only one or occasionally two eggs always caused a recurrence of the latter symptoms, but that was the limit of his tolerance lest he get an acute attack.

Case 2.—A white man, aged fifty, became acutely and violently ill with very severe abdominal cramps and mid-abdominal pain within twenty minutes after eating a hotel dinner. He soon developed severe diarrhea with profuse watery evacuations. These symptoms lasted about six hours and were followed by vomiting with collapse and complete inactivity of the bowels. A clinical diagnosis of intestinal obstruction with ileus paralyticus, on the basis of a possible volvulus or intussusception, was made by the attending physician, and the patient was immediately hospitalized. He gave a history of having had a similar attack six months before at which time he was hospitalized for five days. Abdominal roentgenograms showed no evidence of obstruction.

Several physicians in consultation for an hour considered surgical interference. On questioning the patient, it was revealed that he had suffered from hay fever, asthma, urticaria, eczema, angioneurotic edema, colitis, and severe pruritus ani. However, he was symptom-free as long as he was on an absolute milk-free diet. He had seldom eaten away from home in over twenty years. Just prior to the last two attacks he had eaten out, and on investigation it was found that he had unknowingly eaten foods containing milk. With epinephrine, antihistaminic drugs, and intravenous fluids, he improved rapidly and was up after three days. Before the history of allergy was obtained, he was considered to have had an acute surgical condition of the abdomen.

Case 3.—A white woman, aged forty-five, gave a past history of hay fever, asthma, colitis and chronic dyspepsia or indigestion for twenty years or more. For several years she suffered from frequent acute attacks of severe upper abdominal pain and cramps with "formation of gas pockets" which often required hypodermic injections for relief. Examinations by various physicians were always negative. She had been diagnosed as a gall bladder case with gastritis, duodenitis and pancreatitis, colitis, and gastrointestinal neuroses. During several of her severe attacks surgery had been considered, but she had refused because no definite diagnosis could be made and because she always recovered within a day or two.

On testing, she was found to be sensitive to several pollens and inhalants; food tests proved unsatisfactory. After trial elimination diets, it was found that when she was on a strict milk-free diet, her dyspepsia and colitis cleared up and the acute episode subsided. On several occasions when she ingested milk, symptoms developed in a short time. The severity of the symptoms varied with the amount of milk she had taken.

Case 4.—A white woman, aged forty-five, presented a clinical picture similar to that of the first case, excepting that with acute symptoms of the digestive tract she was also asthmatic. She was known to have a long history of hay fever, asthma, and

symptoms of the digestive tract. Fish always caused an allergic reaction shortly after its ingestion. At the time I saw her for the acute attack in question, she had not eaten fish but there was a platter of fish on the table. Someone had taken a portion of fish, used the same serving spoon to take some mashed potatoes and had left the spoon in the dish. The patient had taken some potatoes with the same spoon and received enough fish protein to cause a very violent reaction which required epinephrine. This relieved the asthma as well as the abdominal pain. Knowing this patient, the diagnosis was not difficult, but her severe abdominal symptoms could easily have been mistaken for an acute surgical condition.

Case 5.—A five-year-old girl had been taking oral pollen extract for treatment of hay fever. One night, after she had helped herself to several large spoonfuls of honey, she developed severe abdominal pain. With this history, epinephrine and Benadryl were administered, and she was relieved of all pain in about one hour. Next day, there were no after effects and she was perfectly well except for a stuffy and runny nose. The honey had, no doubt, contained enough pollen to cause an allergic reaction.

One patient, a fifty-five-year-old male, who at first was thought to have an acute allergic condition of the abdomen, was hospitalized and emergency abdominal roentgenograms were taken. Free air was present under the diaphragm, and, at operation, a perforated ulcer was found. No previous ulcer history could be obtained, but he was known to have been an allergy patient for many years.

Almost any organ of the body can be the shock tissue in an allergic reaction. In the first case, the shock tissue was the liver. An acute liver swelling may cause excruciating pain, as the inelastic hepatic capsule is quickly stretched by the acute allergic edema of the liver tissues. In such a case, there is a great deal of absorption of the offending protein, either completely or partially digested, into the portal circulation, and it is carried directly to the liver. Absorption of an incompletely digested or undigested allergenic substance is more likely to cause acute symptoms of the biliary tract in a previously sensitized liver. In such instances, there is the usual antigen-antibody reaction to account for the allergic condition. In this case, the patient had a tolerance for one or two eggs and suffered no more than the customary dyspeptic symptoms, as previously described. But when four eggs were ingested a more acute reaction occurred. Here, there was probably absorption of native egg protein, as well as an excessive amount of egg, due to the large quantity eaten.

In the second patient, the shock tissue was the intestinal tract. The direct contact of the bowel with the offending food caused a severe enough reaction to lead to symptoms of intestinal obstruction and ileus paralyticus. Here, there was probably a combination of smooth muscle spasm in the intestinal wall and an acute allergic edema of the mucosa.

Although acute allergies of the digestive tract are usually due to foods, they can be caused by ingestion of drugs, oral pollen extracts, and sometimes by parenteral injection of allergenic substances. In this type of

case, the tissues of the digestive tract have been previously sensitized to the offending allergens.

In the differential diagnosis of such cases as described, the history is most important. Nearly all cases will give a history of other allergic manifestations which may give the clue; therefore, to suspect an acute abdomen of being on an allergic basis, the physician must be allergy-conscious. No doubt the etiology of colic and acute symptoms of the digestive tract in children is frequently due to an allergy to food.

During an acute attack, these patients will usually have little fever, if any, even though they are violently ill. The second patient described had a temperature of 100.4° on the second day. The white count is usually within normal limits, or it may be low at first and moderately elevated later. There is usually little or no abdominal muscle spasticity present, although there may be moderate spasticity, but rarely if ever marked or board-like rigidity. An acute abdominal attack with absence of rigidity is strong evidence of an acute medical abdomen rather than an acute surgical abdomen. Other laboratory tests and roentgenograms will usually be negative; however, an eosinophilia may be present in the blood or bowel mucus.

Too much reliability cannot be placed on skin tests because food extracts do not react in a large percentage of the patients with food allergies. Elimination diets are much more satisfactory in determining the offending foods. In the cases herewith reported, the egg- and fish-sensitive patients gave good skin reactions, but neither of the two milk-sensitive patients gave positive skin tests.

It must be remembered that an allergic patient may have an acute abdominal condition due to the usual or common disorders which are in no way related to allergy. In some cases, when a definite diagnosis is not possible, surgery might necessarily be resorted to in order to be certain.

SUMMARY AND CONCLUSION

1. Food allergies may cause acute reactions of the digestive tract and may simulate a perforated ulcer, gall bladder or renal colic, acute pancreatitis, intestinal obstruction and ileus paralyticus, and coronary or mesenteric thrombosis. In such cases, the term "acute allergic conditions of the abdomen" has been used.
2. Five cases are reported as illustrations.
3. When the gastrointestinal tract or liver is the shock organ, an acute attack may be mistaken for an acute surgical abdomen.
4. In any acute abdominal condition, where the diagnosis is not clear, the physician should be allergy-conscious and should question the patient or family about a past history of allergy, as there will nearly always be other allergic manifestations, present or past, to give a clue.
5. In determining the offending foods, elimination diets are more satisfactory in most cases than skin tests.

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FOOD ALLERGY

A Base Diet

MILTON MILLMAN, M.D., F.A.C.A.
San Diego, California

MUCH confusion has existed in recent years as to the relative importance of food allergy. Skin testing for foods has fallen into disrepute in many circles. Elimination diets in the hands of many men have frequently failed. Thus an important phase of allergy loses its lustre because of therapeutic ineffectiveness.

The basis of detecting food allergy is to control the symptoms, then add foods which, if responsible for allergic symptoms, will produce a demonstrable clinical effect. The skin tests play an important part in suggesting what foods to omit initially and what foods to add later. A positive skin test in the presence of a corroborating history is of even greater significance. The skin tests must be interpreted in the light of the other findings in each case. In many of the simpler cases, however, no food tests may be necessary at all, sufficient information being obtained from the history, the basic or other planned diets by trial, and removal of common offenders.

BASIC DIET PRINCIPLE

A basic diet is not a liberal diet, but it should be as adequate as possible in all nutritional aspects. Occasionally the basic diet is not balanced, but this should be followed for as short an interval as possible, new foods being added one at a time, concentrating first on making the diet balanced nutritionally. This diet is planned from foods which are less common offenders and must be modified depending on the history and the elimination of skin-positive foods. If this gives a base line with freedom of symptoms, each new food should be added singly, twice a day if possible, and continued at least four days before it can be considered innocuous and new foods tried.

It must be remembered, in this connection, that one food may cause symptoms for four or five days and that no clinical symptoms may show at the initial servings of the food. A strict knowledge and control of the foods in the diet is essential. The method of preparation is vitally important. We frequently find patients who we believe are following the diet and eating the correct foods, but seasoning them with garlic, tomato, onion, pepper, bacon, and other ingestants.

The diet below is the one I use routinely in my practice. It has the following advantages:

1. The physician can have the diet printed in pads and kept in his desk.
2. One does not have to know many different types of diets, each of which has to be modified anyway.
3. It can be easily balanced nutritionally.

4. The printed list has several different choices of each item so that removal of certain foods is easily accomplished and new additions can be made as indicated.

5. For the initial diet, the physician can and must know each of the foods, as to the frequency of sensitization, nutritional value, methods of preparation, and what the skin test means for each food with his extracts and method of testing.

It is important to note that few patients get the diet as printed. It is modified for each patient depending on the history as obtained by questioning, food check lists, and diary, and when necessary, by skin tests.

THE BASE ALLERGY DIET

Breakfast

Pineapple juice, apple or grapefruit
Coffee
Wheat or oat cereal or rice
Cane sugar
Bread and butter
Evaporated milk diluted with 50 per cent water
Rye Krisp

Dinner

Lamb, steak, veal, or roast beef
Carrots, beets, celery, peas, lettuce, asparagus
Soup—made with above vegetables
White potato or sweet potato
Tea with evaporated milk if desired
Bread and butter
Cane sugar
Evaporated milk diluted with 50 per cent water
Rye Krisp

Supper

Pineapple juice, apple or grapefruit
Coffee or tea
Carrots, beets, celery, peas, lettuce, asparagus
Lamb, steak, veal, or roast beef
Evaporated milk diluted with 50 per cent water
Rye Krisp; bread and butter

Salt is allowed; Crisco used for cooking if butter is not allowed. No substitutions may be made without the consent of the doctor. A food eaten at one meal can be eaten at any other. No seasoning is allowed unless specifically recommended.

Apple and grapefruit are common allergens and are frequently omitted from the preliminary diet. Wheat is a very common allergen and is omitted if there is a question of wheat allergy. It can be omitted from the original trial diet and added in a short time to determine its clinical effect. Beef sometimes causes allergic symptoms, but in general beef, lamb, and veal work out satisfactorily. When wheat is allowed, bread can be included providing that it is egg-free.

Evaporated milk is a good milk for routine use, inasmuch as individuals

allergic to whole milk can frequently tolerate evaporated milk. Butter must be omitted if there is a tendency to milk allergy. Various cheeses can be added to the diet if there is no milk allergy, but different cheeses are made from the milk of several different animals, and this may have to be watched.

Carrots, celery, peas, and beets are potential allergens, but are satisfactory in many instances on the initial routine basic diet. Potatoes and coffee likewise are potential allergens and may have to be removed if an indication exists.

Asparagus, lettuce, and other foods may be substituted depending on the history, skin test, and the general picture.

Only one type of cereal is used initially. If wheat is to be included, wheat cereals can be allowed. In the absence of wheat, oat cereals or rice may be included. Rye Krisp is permitted if wheat is not included in the diet.

With this basic diet, modified as indicated above, many food allergy problems have been solved. After the base line is established, the new foods are added one at a time as previously outlined, leaving the suspicious foods —noted by history, skin test, and avoidance of common allergens—to the last. Vitamins are not added routinely to the initial diet since they too may act as allergenic agents. The multiple vitamins are added shortly after the base line is established or within one to two weeks after the initiation of the diet.

SUMMARY

1. A printed list of foods which can be easily modified into a basic diet has been presented.

2. A discussion of its clinical use has been outlined.

3. Emphasis has been made that there is no perfect elimination diet satisfactory for everyone, but that if the physician has at hand such a list as that described, he can modify it up or down easily as the case requires.

Medico-Dental Building
233 A Street

An item from our national clipping service reports that Jonathan Forman, M.D., F.A.C.A., immediate past president of The American College of Allergists, recently spoke on the subject "Hives" before a session of the Southern Medical Association in St. Louis.

Doctor Forman's new address is 5570 Riverside, R.F.D. No. 2, Worthington, Ohio.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

SEVENTH ANNUAL CONGRESS

The final program of the Seventh Annual Congress of the College, as well as that of the three-day Graduate Instructional Course, appears in this issue. There will be no charge for registration for the scientific program, and all physicians interested in allergy are cordially invited to attend. Since, in addition to these features, there will be thirty-five technical exhibitors comprising the leading pharmaceutical houses and the manufacturers of products of interest to allergists, and scientific exhibits, particularly on ACTH, Pyromen, and bacterial allergy, together with sound pictures as a special attraction, a registration of at least one thousand is expected.

The short instructional course was arranged as a practical refresher course for the busy allergist and also in an effort to stimulate the young allergist to apply the most recent diagnostic procedures and methods of management. It was early discovered, when the College commenced its instructional courses, that the students interested in the practical application of their knowledge to help their patients lost interest when the course was devoted mainly to the fundamentals of immunology, immunochemistry, physiology, pathology, and so forth, because they could obtain this information from standard textbooks. They were not interested in a lofty lecture on investigative observations of many syndromes, infrequently encountered although undoubtedly mediated by immune mechanisms. The students are eager to learn a high quality of diagnosis and treatment which would aid them in their practice. Therefore, the framework of the instructional course this year consists of the methods of history-taking and skin testing, and practical lectures on pediatric allergy, the eczemas, hay fever, asthma, gastrointestinal allergy, food allergy, vernal conjunctivitis, and other allergies met with in the various domains of the body. The status of ACTH therapy will also be presented.

It is interesting that the practical courses are also attended by a number of certified young specialists well trained in their own specialty but not in allergy. They are becoming increasingly aware of the importance which human hypersensitivity plays in disease states.

The Program Committee purposely omitted lecturers on highly controversial subjects, who are sincere but overenthusiastic advocates of procedures which are still without sufficient evidence of their validity.

The Edgewater Beach Hotel is equipped to handle comfortably a large convention, and its isolation from the loop district has many advantages.

These short conventions are planned mainly for the exchange of ideas in the field of allergy and to promote cordial relations among its members, including some relaxation; they have never been planned as a vacation for the busy physician.

The scientific program will open with the general session on Monday morning. The remainder of this time, aside from the presidential and guest speakers' addresses and the business meeting, will be taken up with sections on psychosomatic, pediatric, otolarynologic, and dermatologic allergy. The final afternoon will be devoted entirely to a panel on rheumatism and arthritis.

Those who have not made reservations should do so at once, directly with the Edgewater Beach Hotel, Sheridan Road, Chicago, stating the exact time of arrival and departure and whether a single or double room is desired.

MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

(Continued from Page 764)

ferent kinds of fungi associated with ball moss as a substrate can probably best be explained by the peculiar nature of the tissues of the plant which would seem in part, at least, to be due to water-holding ability (hygroscopicity).[1]

When the large amount of surface thus provided by each moss plant as a likely substrate for the growth of fungi in large numbers and of diverse kinds is considered—together with the fact that, being air-borne, these fungi may be potential respiratory allergens—it would seem, therefore, that in analyzing an environment for sources of fungi, the Tillandsia mosses constitute possible hazards for sensitive individuals.

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Progress in Allergy

ACTH AND CORTISONE IN THE MANAGEMENT OF THE HYPERSENSITIVITIES, WITH PARTICULAR REFERENCE TO BRONCHIAL ASTHMA

A Review of Clinical and Laboratory Studies

MAURICE S. SEGAL, M.D., F.A.C.A., and J. AARON HERSCHFUS, M.D.
Boston, Massachusetts

THE advent of potent purified preparations of cortisone and pituitary adrenocorticotropic hormone has revolutionized the management of a wide variety of chronic illnesses. Spectacular control of symptomatology and remissions has been described in a wide diversity of disease entities since the epoch discovery by Hench and his associates[18,19] of the use of cortisone and ACTH in the treatment of rheumatoid arthritis and of cortisone in rheumatic fever. Recently Thorn and his associates[44,45,46] in a comprehensive series of papers reviewed their laboratory and clinical observations, as well as those of other investigators, with ACTH and cortisone. Their discussion of these hormones included the preparation of ACTH and cortisone, the mechanism of action, metabolic effects, immunologic properties, toxicity and undesirable effects, and also clinical indications. They divided the disease entities which have been treated with ACTH and cortisone into three main groups: most useful, may be useful, and of questionable value. In addition, they listed the diseases in which these agents are of no value and may even be detrimental. Prominent in the first two groups were the hypersensitivities, namely, urticaria, serum sickness, exfoliative dermatitis, Loeffler's syndrome, status asthmaticus, and vasomotor rhinitis.

The limited (initial) supply, the prohibitive cost of these powerful therapeutic agents, and the impetus of Hench's work directed their earliest application to the management of a variety of collagen disorders: namely, rheumatoid arthritis, acute rheumatic fever, lupus erythematosus disseminatus, dermatomyositis, periarteritis nodosa, scleroderma, et cetera. Somewhat later their use in hypersensitivity states followed. The therapeutic results in the more common hypersensitivities have been found to be even more spectacular than those observed in the collagen disorders.

A series of encouraging preliminary reports describing the use of ACTH and cortisone in the asthmatic patient have appeared. Bordley et al[3,4] wondered whether the dramatic responses to cortisone and ACTH observed in rheumatoid arthritis and rheumatic fever might not result from some change induced by these agents upon the mechanisms of hypersensitivity, inasmuch as Rich[29] had clearly shown that the basic anatomic lesions of the rheumatic diseases could be reproduced experimentally in animals by the induction of allergic reactions. They were impressed also by the striking and rapid improvement which followed the use of ACTH in a patient with exfoliative dermatitis from iodine.

In their preliminary reports[3,4] they discussed the results of therapy with ACTH in four patients with lupus erythematosus disseminatus, seven patients with bronchial asthma, and two patients with acute (serum type) penicillin reactions. The clinical response in all of these patients was most favorable. The seven patients with bronchial asthma were of the severe chronic type; five were believed to be of the

Dr. Segal is Clinical Professor of Medicine, Tufts College Medical School, and director, Department of Inhalational Therapy, Boston City Hospital.
Dr. Herschfus is a research fellow in medicine, Tufts College Medical School.

intrinsic type, and two of the type due to combined intrinsic and extrinsic factors. Their ages varied from twenty-six to sixty-three years, and the duration of the bronchial asthma from five to twenty-three years. The patients had been in severe distress for months and had obtained only partial and brief relief from established therapy. When ACTH therapy was started, all other medications (save placebos) were discontinued. Unequivocal benefit was noted in from four to forty-eight hours. The dosage schedules employed in this series appear to have been comparatively low. Twenty to one hundred milligrams daily in divided doses at six-hour intervals were administered. Therapy was continued from nine to twenty days. The total amount of ACTH given varied from 360 to 775 milligrams. All signs and symptoms disappeared in from one to eight days except in one patient, six months pregnant, who felt entirely relieved but in whom some rhonchi persisted. Spirometric tracings disclosed release from the relative obstruction to outflow at the time of symptomatic relief.

The authors described interesting changes in the para-nasal sinuses. There was rapid disappearance of edema and a change in color to bluish pink in those patients with pale edematous polypoid nasal membranes. The breathing space was greatly enlarged. The lymphoid tissue, when edematous, likewise assumed a normal color, and the crypts became more prominent. There was no gross change (shrinkage) in volume of the lymphoid tissue present. Two of the patients had polyps which completely obstructed the nose; the polypi began to shrink before the fifth day of treatment, and disappeared entirely in one patient and almost disappeared in the other. Polypi reappeared in one patient in twenty-three days, and in the other the remission lasted one month. Three patients with antral clouding by x-ray presented normal sinus x-rays after ACTH therapy. Similar changes to a less marked degree were observed by Rose[30] and Segal et al.[39]

Rose et al[30,20] made a series of preliminary reports describing their observations on the effect of ACTH in one case of Loeffler's syndrome, one case of tropical eosinophilia, and six cases of bronchial asthma. The first case, a man of forty-four, had a classical Loeffler's syndrome with pulmonary infiltrations and an eosinophilia of 2865/cu mm before treatment. He was given 140 mg of ACTH in four divided doses over a four and a half hour period. The second case, a young Indian student, aged twenty-one, had typical changes in chest x-rays and marked eosinophilia. The total white count was 46,630 of which 39,130 (83.9 per cent) were eosinophils. He received 120 mg in two divided doses over a four and three-quarter hour period. A transient increase in total circulating leukocytes occurred in both cases. A virtual disappearance of eosinophils, from 2865/cu mm to 54/cu mm, was observed in ten hours in the patient with Loeffler's syndrome. The circulating eosinophils did not return to their pre-ACTH level over a subsequent two-year period of observation. A complete clinical and x-ray remission of the disease followed and has persisted. The well-known tendency for spontaneous remission in Loeffler's syndrome was appreciated by the authors. In the patient with tropical eosinophilia, however, although a decrease in total eosinophils (from 39,130/cu mm to 25,700/cu mm) occurred by the twelfth hour, it did not persist. The difference in the response of the eosinophil count to ACTH in these two disorders was not explained. The pulmonary infiltrations persisted, and the patient was then treated with mapharsen. A complete remission of symptoms followed this therapy. The duration of ACTH therapy may have been inadequate. Of further significance is the fact that the authors were able to confirm their previous observations that no correlation existed between blood histamine and fluctuations of eosinophils in studies on these two patients. Of greater significance was the fact that the histamine values were all within normal range, despite the marked eosinophilia and subsequent eosinopenia. This appears to corroborate that the eosinophil in man is not responsible for carrying histamine.

Rose and his associates[36] had previously studied the metabolism of histamine and

its specific enzyme histaminase in adrenalectomized rats, and in normal, asthmatic, and pregnant patients. Encouraged by their recent observations of the relationship of asthma to Loeffler's syndrome which is benefited by ACTH, and the demonstration by Thorn et al[43] of the eosinopenic effect of ACTH in humans with intact adrenals, they then extended their preliminary observations with ACTH to asthmatic subjects.[30,35,36] They treated six patients with severe intractable bronchial asthma of three to eight years' duration with ACTH.[30,35] One patient had in addition rheumatoid arthritis and another had periarteritis nodosa. Extensive metabolic studies were carried out while the patients were observed under conditions of controlled caloric and electrolyte intakes. After the sixth hospital day they were given intramuscular injections of sterile water, at six-hour intervals. ACTH was substituted for the latter on the tenth hospital day, on the same time schedule. The first two patients received 150 mg daily for two days and then 100 mg for two more days, making a total of 500 mg over the four-day period. The next four patients received 100 mg daily for three days, 75 mg daily for two days, and 25 mg on the sixth day, making a total of 475 mg. The patients received non-specific medication such as epinephrine or aminophyllin when necessary.

The signs and symptoms of rheumatoid arthritis and periarteritis nodosa in two of the patients were greatly improved with a complete remission of the bronchial asthma. The vital capacity and maximum breathing capacity improved in all of the patients. There was shrinkage but no complete regression of the thickened polypoid nasal and antral mucous membranes. Unfortunately, the longest remission observed was one month, with return of symptomatology to its former severity by the end of the sixth week. There was complete remission in four patients within forty-eight hours, and in two patients there was considerable improvement but no complete remission.

Rose[31] later discussed his experiences in ten patients with manifestations of hypersensitivity, including urticaria, allergic rhinitis, asthma, periarteritis nodosa, and acute disseminated lupus erythematosus. Satisfactory clinical improvement was noted in six patients. The longest remission noted was six weeks.

Randolph and Rollins[26,27] anticipated usefulness of ACTH in allergic states because of the relationship of the pituitary-adrenal axis to the immune reaction, and the eosinopenic effect of ACTH. They discussed their experiences with ACTH in thirteen patients with allergic syndromes. Ten of the eleven asthmatic patients obtained considerable relief (50 per cent to 100 per cent range) for one week to five months following a single brief course of therapy. The dose schedule was 25 mg every six hours. The total dosage ranged from 125 to 325 mg (lower than that employed by Rose et al and Bordley et al). Clinical improvement was noted four to six hours after the initial 25 mg dose in three of their first four patients. These three remained markedly improved for twenty-one days after treatment was stopped. Mild residual asthmatic symptoms, which did not require medication after the first day of treatment, persisted. In each patient, however, there was a gradual return of asthma during the fourth week requiring the use of symptomatic measures for relief. The first three patients were then re-hospitalized because of bronchial asthma of the former severity, and a second identical course of ACTH was followed by similar improvement.

Randolph and Rollins found ACTH least effective in patients with pulmonary emphysema and scarring from pleurisy and empyema. They noted striking improvement in the reactivity of several patients sensitized to food allergens (oral and inhalant). Three patients with asthma were known to be clinically sensitive to several food allergens capable of producing asthma. Deliberate feeding tests repeated during or immediately after stopping ACTH therapy produced but transient accentuation of symptoms or showed complete tolerance of the food allergen. One pa-

tient with atopic dermatitis, reproducible by wheat ingestion and curable by wheat avoidance, showed a striking improvement which lasted for five days after receiving 350 mg of ACTH administered over a fifty-hour period. During the week following ACTH therapy, the dermatitis recurred to a greater degree of severity than previously observed. Another patient with a similar atopic dermatitis, highly sensitive to corn ingestion, was successfully treated with a total of 225 mg of ACTH administered over a three-day period. Improvement continued in spite of the continual ingestion of corn products during ACTH treatment. Following the course of ACTH therapy, corn was omitted and this improvement was maintained for ten days. Unfortunately, as with the first patient, the extensive dermatitis reverted to a greater degree of involvement than existed prior to these observations. A third patient, known to be violently sensitive to wheat, developed cramps and diarrhea following its ingestion. Prior to therapy with ACTH, she was ill for three weeks with colitis. She was given a course of ACTH, receiving a total dosage of 325 mg over a period of eighty hours. She became symptom-free on the third treatment day and was able to tolerate a meal of wheat gruel one day after cessation of ACTH therapy. She subsequently tolerated a general diet including wheat and other food allergens for a period of twelve days, and she gained weight. Abdominal cramps and diarrhea then recurred but were controlled for another week by excluding wheat from the diet. A fourth patient presenting a violent reaction (headaches, rhinitis, and gastrointestinal reactions) to the inhalation of cooking pork had relief of symptoms after receiving 33 mg of ACTH. The authors treated three additional pork-sensitive patients successfully with ACTH. Conn,[8] in discussing these observations, briefly mentioned twice relieving food urticaria in a boy with 25 mg doses of ACTH.

The authors also reported striking amelioration of ragweed hay fever symptoms in four patients and complete protection for the remainder of the season in three of these patients with ACTH. The dosage ranged from a total of 125 to 250 mg administered over a twenty-four- to fifty-four-hour period, between August 31 and September 11, 1949.

Segal et al[38,39] administered twenty-seven courses of ACTH therapy to twenty patients with severe chronic bronchial asthma over an eight months' period (January through August, 1950). There were fourteen females and six males in this series. The patients' ages varied from fifteen to seventy-two. They were all seriously ill with a wide variety of associated and related defects: hay fever, atopic eczema (aureomycin), nasal polyps, sinusitis, severe bronchitis, various degrees of emphysema, cor pulmonale, hypertension, cerebral arteriosclerosis, and diabetes mellitus. In general, higher total doses than previously reported were employed. The initial dose of 40 mg was repeated in six hours. It was followed by 20 mg every six hours until lasting benefit had been observed for two days. If improvement continued, the time interval was then increased to every eight hours for one to two days or longer. Usually after the fourth day of therapy the time interval was further increased to every twelve hours until the time of discharge. The total doses of a single course of therapy varied from 240 mg to 900 mg and the duration of therapy from two and a half days through nineteen days.

The immediate therapeutic effect in the twenty-seven courses administered was as follows: failure, two; fair, four; good, three; and excellent, eighteen. The continued therapeutic effects was as follows: failure, three; fair, eight; good, ten; and excellent, six. Unfortunately the period of remission was generally short. Repeated intensive courses of therapy were frequently found necessary and appeared more effective than attempts at maintenance therapy. Failure to respond to the same degree was noted sometimes after the second course of therapy. The authors cautioned that repeat courses of therapy should not be employed too freely, inasmuch as the nature of the repeated remission and the effects of repeated hormonal overstimulation might not be free of hazard. Clinical and postmortem evidence was

presented that the possible mechanism of death in bronchial asthma may be due to failure in the homeostatic mechanism (the hypothalamus-pituitary-adrenal axis) to provide an adequate level of ACTH for the secretion of sufficient adrenocorticoids. The vigorous use of ACTH ("therapeutic adaptation") in this type of patient at such a critical period may prevent death by compensating for this imbalance.

In addition to the above preliminary reports, several other case reports have appeared. Kanee et al[24] administered ACTH to a fourteen months' infant who had had eczema since the age of three weeks and asthma since the age of twelve weeks. Ten mg was administered every six hours. Improvement of the eczema was noted within twenty-four hours and complete clearance in forty-eight hours. The clinical remission was still evident eight weeks after cessation of therapy.

Elkinton et al[10,11] in their study of the effects of ACTH therapy included a five-year-old boy with status asthmaticus who showed remarkable improvement. They observed the development of resistance to ACTH in two patients. One patient with acute rheumatoid arthritis obtained less relief from the drug as time went on, though the dose was steadily increased until its use had to be discontinued because of the appearance of Cushing's syndrome. Another patient who was being treated for lupus erythematosus disseminatus, after having responded to ACTH initially, had recurrence and progression of symptoms, despite 200 mg daily. This patient died. Serologic studies indicated that some type of antibody to the adrenocortical preparation was present.

Forsham,[14] in an interesting discussion of various types of sensitivity to ACTH, comments on the appearance of hives, anaphylactoid reactions, and the decreasing activity of similar doses in the same patients. Preliminary observations in a case demonstrating diminished effectiveness of the same daily dose showed the presence of ACTH neutralizing antibodies. Variability of lot potency and changes in the responsiveness of the adrenal cortices were considered and ruled out. Furthermore, he noted less resistance to the hormone developing with continued ACTH administration than when the course of treatment was interrupted for one to two weeks.

Thorn et al,[44,45,46] in their review articles previously referred to, treated three patients with severe chronic bronchial asthma, employing doses of 10 mg of ACTH every six hours. All the patients showed marked improvement for five to seven days after the cessation of therapy. A second patient on a similar schedule had no recurrence of asthma for one month after cessation of ACTH. The authors concluded that doses of 10 mg every six hours were capable of alleviating the asthmatic symptoms in the majority of the patients but that improvement may not be maintained after therapy has stopped. They considered that ACTH was the drug of choice in cases which had become irresponsive to the usual therapeutic measures and furthermore that restoration of the therapeutic effectiveness of other more common agents would be noted with the ensuing remission.

These authors also treated one patient with severe, persistent vasomotor rhinitis of two years' duration with ACTH, employing 10 to 12 mg every six hours for ten days. Previously the usual antihistaminic agents and hyposensitization had been only slightly effective. Improvement in nasal patency and rhinorrhea was observed within twenty-four hours after starting ACTH. The signs and symptoms of allergic rhinitis disappeared after ninety-six hours. Improvement has persisted for three months to date.

Samter[37] treated six patients suffering from bronchial asthma with ACTH. Four patients showed satisfactory improvement and two patients significant improvement. Details of management and clinical response were not given. The improvement noted was described as proportional to the metabolic and hematologic changes. If a patient failed to show an increase in the urinary excretion of 17-ketosteroids and 11-oxycorticosteroids, and a decrease in the number of circulating eosinophils, he also failed to show clinical improvement. Changes in excretion of 11-oxycorticoste-

roids and in breathing reserve as effected by ACTH are shown to be similar under the influence of fever and an unknown stimulus.

Astwood and his associates[2] prepared three different, therapeutically active preparations of corticotrophin (ACTH) and reported their observations on forty-two patients treated for a variety of diseases. In this preliminary report they treated five patients with bronchial asthma. The patients' ages ranged from nine months through sixty-seven years. The adult patients were given 20 mg of preparation A at six- to 8-hour intervals for five to twelve days. The infant was relieved by 10 mg of preparation B every six hours but not by 5 mg of preparation A every twelve hours. Convulsions developed while using the large dose and did not return with the lower dose. Three patients who had been in a state of constant asthma for six to eight months were promptly and completely relieved of all signs and symptoms of bronchial asthma. A man, aged forty-four, suffering from periodic attacks of bronchial asthma, was moderately benefited. A woman, aged forty-nine, with mild asthma improved, but accompanying rhinitis and sinusitis persisted. A sixth patient, aged thirty-five, with allergic rhinitis received 80 mg daily of preparation A for three days and had a complete remission which persisted as long as followed (time not mentioned).

Brown[5] recently made a concise review of selected papers dealing with ACTH, its pharmaco-physiology in rats and humans, and the clinical results obtained by several investigators in a variety of disorders. He concluded that in ACTH we may find a powerful remissive agent for the acute hypersensitivities (penicillin and drug reactions) and a temporary remissive agent for the more chronic disorders (hay fever and bronchial asthma). Brown wisely encourages the continued search for and elimination of the basic sensitivities and urges that the internist-allergist become more familiar with the metabolic and endocrine relationships involved with ACTH therapy.

Burrage[6] in a recent, succinct review of the progress in allergy cautions that despite the dramatic temporary cessation of symptoms observed with ACTH in allergic diseases, one should not hastily conclude that the problem of allergy is about to be solved. The fundamental process by which ACTH and cortisone affects these diseases must first be determined.

* * *

Observations on the effect of cortisone on bronchial asthma and hay fever have been very limited. Randolph and Rollins[28] treated five patients with bronchial asthma with cortisone. In four patients they made comparative studies of cortisone and ACTH therapy. They found cortisone partially effective in relieving the symptoms of intractable asthma but, in the doses employed, less effective than ACTH. Both cortisone and ACTH caused the same hematologic changes. One patient obtained no relief with cortisone but had a satisfactory response from cortisone with supplemental vitamin C intravenously. Another patient on vitamin C orally relapsed after several days. When given cortisone with vitamin C, he exhibited a more complete and sustained clinical response. Segal et al[39] were unable to potentiate or prolong the effects of ACTH with intravenous cevitamic acid (4 grams daily for as long as five days in several patients).

Carryer et al[7] observed the effect of cortisone under controlled conditions in three patients suffering from hay fever and seasonal asthma due to ragweed pollen. The patients received 100 mg of cortisone or 100 mg of cholesterol crystals (control) daily for four weeks. The results with the cortisone were considered beneficial. Each patient experienced prompt relief. The symptoms of bronchial asthma were relieved more quickly than the hay fever symptoms. Only mild, transitory symptoms persisted after three days of cortisone. Symptoms recurred shortly after cessation of treatment.

In another study (limited to three patients) cortisone did not prove as effective as ACTH in controlling the asthmatic state or in inducing an adequate eosinopenia.[39] One patient received 300 mg of cortisone over a three and a half-day period, immediately following an initial unsuccessful remissive attempt with ACTH. There was no clinical improvement. The previously obtained eosinopenia could not be maintained. A second patient received a total of 510 mg of ACTH during eight days with complete amelioration of respiratory symptoms except for exertional dyspnea, and with considerable improvement in his associated rheumatoid arthritis. Because of insufficient supply of ACTH, he was then given cortisone, 150 mg in three days. This was ineffective in controlling either his respiratory symptoms or his joint manifestations. As with the first patient, the eosinopenia could not be maintained. A third patient was given cortisone initially in an attempt to alleviate severe status asthmaticus. Thirty mg intramuscularly were administered every eight hours for six doses (180 mg) with no clinical improvement or drop in the control eosinophil level. ACTH was then substituted for cortisone. He received 420 mg over six and a half days with an excellent remission and eosinopenia. This remission lasted for six weeks. During this period he was given small (25 mg) weekly doses in an attempt at maintenance therapy. ACTH was abandoned after two nearly fatal anaphylactoid reactions. About seven weeks later, the patient developed a most severe degree of status asthmaticus and cor pulmonale requiring hospitalization. He was refractory to all medication. An intensive course of cortisone was begun and he received a total of 600 mg until his death on the second hospital day.

One cannot help speculating whether ACTH, which was not administered at this time because of the previous toxic reactions, might not have been effective. The studies by Forsham et al[15] on the functional state of the adrenal cortex during and following ACTH and cortisone therapy revealed that cortisone therapy (100-200 mg daily) suppressed both adrenal cortical activity and the response to ACTH for up to ten days after therapy. When ACTH (100 mg daily) was added to the cortisone therapy, an additive effect rather than suppression of the 17-ketosteroids was observed. When only 40 mg of ACTH was used daily, 100 mg of cortisone a day failed to show a rise in 17-ketosteroid excretion. This suggested to the authors that cortisone acts through pituitary ACTH inhibition, rather than through any inhibitory effect on the adrenal cortex itself.

STUDIES CONCERNING THE MODE OF ACTION OF ACTH AND THE NATURE OF THE IMMUNE REACTION.

A masterful study in rabbits by Harris and De Groot[17] postulated a neurohumoral mechanism (adrenergic in nature) by which stimulating influences from the hypothalamus may be transmitted to the anterior pituitary gland, with a resultant release of ACTH. This phenomenon of activating the pituitary through a peripheral sensory stimulus was applied in an extremely interesting study by Hume and Wittenstein[23] in a series of operations on dogs. The eosinopenic response to surgical stress, before and after making electrolytic lesions in the hypothalamus, was observed. They concluded that the following factors were significant in the release of ACTH from the anterior pituitary following stress: (1) An intact hypothalamus is essential. (2) Lesions in the hypothalamus abolish or decrease the response even in the presence of an intact pituitary-adrenal cortex. (3) The hypothalamic control of the pituitary seems to be mediated by means of a hormonal mechanism, inasmuch as severing of the nervous and vascular connections between the intact hypothalamus and pituitary did not abolish the eosinopenic response to stress. (4) Complete sympathectomy did not alter the response; so that neither epinephrine nor sympathetic fibres to the pituitary are essential to pituitary release of ACTH following stress.

A marked release of ACTH from the pituitary followed remote control stimulation of the hypothalamus in a sympathectomized animal, and finally (5) preliminary work with extracts of beef hypothalamus seemed to indicate the presence of a special pituitary-stimulating hormonal substance.

Rose and his associates[30] had previously demonstrated in rats the direct relationship between the adrenal cortex to the metabolism of histamine and its specific enzyme histaminase. The tissue and blood histamine was markedly increased and the mechanism for the destruction of histamine was impaired following adrenalectomy. They were able to fully restore these changes by the administration of cortin but not by desoxycorticosteron.[32] Selye[40] more recently has shown that the administration of DOCA intensifies the anaphylactoid state, whereas cortisone or ACTH protects. Cortisone and ACTH also protected sensitized adrenalectomized rats to the lethal anaphylactic reactions of egg white injections.

Spontaneous remission of bronchial asthma during pregnancy has been observed by most investigators. Venning[47] reported an increase of urinary glycocorticoids, and Ahlmark[1] found an increase in plasma histaminase during pregnancy. Rose et al[34] had previously shown that compared to the normal pregnant woman, the level of plasma histaminase is impaired in the asthmatic who fails to have a remission during pregnancy. They[33] also found a higher histamine content in the shock organs (lung, skin, or mucous membranes from nasal passages and antra) in allergic patients as compared with those from normals. Histamine and histidine[30,35,36] excretion in the urine was measured before and after ACTH administration, and nearly all the patients demonstrated a marked increase in the histidine output with levels sometimes reaching as high as those seen in pregnancy. This was noted within twenty-four hours after the administration of ACTH, and the values promptly returned to normal after withdrawal of ACTH. An early report[30] on six asthmatic patients indicates an excess of histamine in the urine before treatment. Urine histamine disappeared in five but increased in the sixth patient, who did not have a complete remission. The urinary 17-ketosteroids were increased in five patients, but failed to rise in the sixth patient, in whom there was also a delay in urine histamine decrease, as well as a failure of eosinopenia.

The reader is referred to the masterful presentation by White[48] summarizing the experimental evidence for the role of the adrenals in the immune mechanism and the role of the pituitary-adrenal axis in the allergic state. White discussed the role of the reticulo-endothelial cells involved in the immune mechanism. He cited evidence of lymphocytic dissolution following increased pituitary-adrenocortical secretion and evidence that in the immunized animal one of the constituents of lymphocytes is antibody globulin. Additional evidence was presented that the adrenals are involved in the maintenance of the tonus of the ground substance of the mesenchyme. Tissue permeability (intradermal spreading) was decreased by injections of adrenocortical extracts. Implications of the role of the adrenals in resistance against invasive organisms and toxins are thus apparent.

The possible implication of the inhibition of mesenchymal permeability, as described by White, as a *modus operandi* of ACTH therapy in bronchial asthma was also referred to by Samter in the same journal issue.[37] The latter discussed in an engaging manner a series of facts and speculations concerning the physiologic mechanism involved in allergic manifestations and possible mechanism of ACTH in the allergic state. He raised the question as to the possible relationship between tissue permeability and ACTH. He was able to demonstrate protection with ACTH against the bronchoconstrictor effects of histamine aerosols (number of patients not mentioned). Similar protection has been noted by Rose et al[35] and Segal et al.[39] Samter assumed from this observation that the permeability of the (connective tissue) barrier had changed with ACTH therapy. On the basis of the evidence

presented, he further suggested that ACTH, through the release of corticosteroids from the adrenals, alters the mesenchyme of the bronchial shock tissue, rendering it less vulnerable to specific and nonspecific agents. The similarity in action in the allergic state between fever (real and artificial), ACTH and cortisone also suggests a more fundamental homeostatic mechanism rather than drug-like action. Further confirmation of this point of view may be found in the observations by Herschfus et al,[21] wherein they were unable to demonstrate any significant antihistaminic or anticholinergic properties with single large doses of ACTH in the asthmatic subject. The repetitious eosinopenia induced by typhoid fever in a series of patients with bronchial asthma, as striking as that observed with ACTH, would appear to suggest a similarity in action between ACTH and fever.[22] Promised investigation by Samter of other factors that determine the shock organ in the allergic patient, independent of pituitary-adrenal regulations, will be eagerly awaited.

The ability of ACTH or cortisone to modify antibody production was tested by Mirick[25] in twelve patients treated for bronchial asthma or other related diseases. The patients were vaccinated with pneumococcal polysaccharides, and serum was obtained at several-day intervals for several weeks. Antibody titer appeared promptly and in as high a titer in the eight patients who were treated with ACTH and in the four who were treated with cortisone as in the controls. The degree of induced skin sensitivity to pneumococcal polysaccharides was depressed in some patients during treatment. A consistent drop in the gamma globulin of the sera was observed in all but one of the treated patients, even though specific antibody titer against the pneumococcus was increasing all the time.

Forsham[14] mentioned that in four patients with lupus erythematosus disseminatus, an elevated gamma globulin was found which was markedly depressed by ACTH administration. In the same discussion an interesting curve drawn from one of these patients reveals a profound fall of gamma globulins when ACTH becomes effective with a definite rebound after cessation of therapy. A remarkable, constant inverse relationship of the complement titer to the gamma-globulin concentration was observed in all of these cases. Finland et all[13] in an important contribution described the appearance of specific (pneumococcal type 8) agglutinins at the usual time in a patient with pneumococcal pneumonia successfully treated with ACTH.

Soffer et al[42] attempted to block the Schwartzman reaction in rabbits with ACTH. ACTH did not influence the phenomenon when it was injected before the preparatory intradermal sensitization. However, when administered before the provocative intravenous injection, the Schwartzman phenomenon was completely inhibited in eight of the ten rabbits tested. The control groups showed a high incidence of reaction, and surgical pituitrin failed to inhibit the reaction.

Finally, numerous studies have appeared, attempting to shed some light on the immune mechanism and the inter-relationship of the hypothalamus-pituitary-adrenal axis in allergy by noting the effect of ACTH on skin testing, passive transfer studies, histamine metabolism, and protection against the bronchoconstrictor effects of histamine.

No consistent changes were observed in skin testing of the direct type in the earliest reports on ACTH therapy in the hypersensitivities. Bordley et al[4] reported a definite diminution in skin sensitivity to inhalant and bacterial antigens in one patient. The responses returned to their original levels in three weeks. Similar changes were not observed in skin tests of the direct type[30,39] and also in passive transfer tests[39,49] in other series of treated patients. On the other hand, Favour et al[12] have demonstrated that under the action of ACTH, the hypersensitivity phase of the reaction to tuberculin (delayed type) may be abolished. Guinea pigs sensitized to tuberculin showed disappearance of the tuberculin skin reaction while on ACTH.

Following discontinuance of ACTH, it reappeared. Suitable controls all showed a good tuberculin reaction. Complete correlation was obtained by the use of a lympho-lysis test, in which lymphocytes from tuberculin-sensitized guinea pigs were lysed by adding tuberculin *in vitro*. The lymphocytes were lysed before and after ACTH, but not during ACTH administration. The hazards of such a change in hypersensitivity in the treatment of human tuberculosis remain to be determined.

Zeller et al[49] made a detailed gross and histologic study of scratch and intradermal tests on two ragweed-sensitive patients successfully treated with ACTH. The reactions to scratch and intradermal tests and successful passive transfer studies were not altered after ACTH therapy. A histologic study of the allergic wheal revealed eosinophilia in the inflammatory exudate as the most constant finding. Following the blood eosinopenia induced by ACTH, the wheal eosinophilia is reduced in the treated patient, but the latter phenomenon was not transmitted to the passive transfer recipients. From one hay fever patient with ragweed whealing, a biopsy taken after epinephrine showed a drop in tissue eosinophilia. Antihistaminics, orally or locally, inhibited ragweed or histamine whealing, but ACTH failed. They concluded that ACTH alters the hypersensitivity state of the clinical shock organ without influencing gross skin effects, whereas the antihistaminics alter both.

Bordley et al[4] tested four of their treated patients for sensitivity to histamine. All responded normally to intracutaneous histamine and likewise to intracutaneous curare both locally and by increased gastric flow of free HCl. They concluded that these tissues at least can produce histamine (or histamine-like substances) and react to it in the normal fashion while the patient is receiving ACTH.

Herschfus et al[21] demonstrated that single large doses of ACTH did not prevent histamine- or methacholine-induced asthma in asthmatic subjects, as has repeatedly been noted with adrenergic or histaminolytic agents and aminophyllin. On the other hand, the abnormal sensitivity of the asthmatic patient to injected histamine was lessened or abolished by treatment with ACTH (repeated injections).[39] Similar studies with ACTH in induced asthma were carried out by Curry et al.[9] Significant protection against the action of histamine and methacholine was not achieved with single doses of 50 to 100 mg of ACTH. These studies would indicate that ACTH probably does not relieve bronchial asthma through an antihistaminic or anticholinergic action.

Rose et al[30,35] demonstrated that the ability of histamine or methacholine aerosols to produce dyspnea with bronchoconstriction was blocked in four patients by ACTH therapy. One of these patients also reacted less to the effects of aerolized grass pollens. We observed a similar marked improvement to the bronchoconstrictor effects of dog dander in one of our ACTH-treated patients.[39] Nevertheless, this patient did not derive satisfactory clinical relief from ACTH and cortisone therapy, nor did ACTH protect her against the effects of histamine intravenously.

Friedlaender and Friedlaender[16] confirm the inability of ACTH to alter histamine and skin testing whealing in humans, and they were unable to protect guinea pigs against histamine and mecholyl-induced bronchospasm by single or multiple injections of ACTH.

The explanation for the variability in blocking by ACTH of the effects of a variety of stressors (histamine and allergens) at different target sites (skin and respiratory tract) is not apparent. However, these studies appear to demonstrate the lack of direct antihistaminic and anticholinergic properties as well as the lack of drug-like action of ACTH itself.[4,9,16,21,30,37,49]

This review would be incomplete without reference to the splendid contributions by Hans Selye[41] and the progressive development of his concept of the response of the body to stress, the general adaptation syndrome (G-A-S). The human

being is able to withstand a wide variety of acute environmental stresses such as hypoxia, trauma, infection, hemorrhage, burns, fear, anger, anaphylaxis, histamine release, et cetera, by a complicated neurohumoral adaptive mechanism. The response to the stresses and strains of life are usually met with adequate adaptive responses (G-A-S) in which corticotrophin production plays an important part. Stress acts through the G-A-S, the latter developing in three stages: the alarm reaction (shock and counter-shock), the stage of resistance, and the stage of exhaustion. Adaptability and resistance to stress are fundamental prerequisites for life. Diseases of adaptation may follow in the wake of maladaptation (hypo-, hyper-, or dys-adaptation).

Selye's concepts attempt to explain how the G-A-S response may lead to a variety of unrelated diseases which are amenable to adrenocorticotropic hormones. The evidence is accumulating that bronchial asthma should be regarded as one of the diseases of adaptation (hypo-adaptation)—a derailment of the G-A-S. Selye gives evidence that the anti-asthmatic effect of the gluco-corticoids and of adrenergic substances suggests that the endogenous discharge of adrenal hormones may be a normal defense mechanism against the allergic response to stimuli. An adequately functioning hypothalamus-pituitary-adrenal axis is necessary for continued adaptation.

SUMMARY

The adrenocorticosteroids appear capable of intervening in the acute and chronic manifestations of hypersensitivity of body cells to bacterial and non-bacterial sustances. They appear to inhibit the altered reactions of cells, probably at the mesenchymal level, rather than inhibit any of the direct toxic effects of the sensitizing agents themselves. Therapeutic benefit is achieved by creating a state of hormonal excess. "Therapeutic adaptation" for a state of hypo-adaptation (Selye) is thus possible with these agents. The exact mechanism of this action is still not understood.

The goal of all therapy in the patient with serious bronchial asthma is the production of a prolonged remission. Frequently, when such a remission occurs, one is unable to explain its genesis. Just as often one cannot bring about a second remissive episode employing the same procedure. ACTH apparently offers a way to cause such a remission more consistently than by any other therapeutic regimen.

However, improvement with ACTH frequently may be maintained for but a short period; prolonged administration is not feasible; there is some evidence that in relapse the symptoms of some types of hypersensitivity may recur with greater severity than before; and finally, repeated stimulation of the hypothalamus-pituitary-adrenal axis may not be desirable. To what extent undesirable physiologic and toxic effects which follow in the wake of ACTH and cortisone will limit their usefulness in the management of the more chronic allergic disorders remains to be revealed.

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PREGNANCY AND THE TREATMENT OF HAY FEVER, ALLERGIC RHINITIS AND POLLEN ASTHMA

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method (found best) once in two weeks. In addition, some patients will require small doses of a tried and established antihistaminic drug (Pyribenzamine 25 mg) for more complete relief. Attention must also be given to inhalant antigens, and desensitization must be carried out where indicated. All the cases reported here were delivered by various local obstetricians and experienced no flare-ups or complications.

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ACUTE ALLERGIC CONDITIONS OF THE ABDOMEN

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6. In some cases the administration of epinephrine and antihistaminic drugs will serve as a therapeutic as well as a diagnostic measure.

7. It must be remembered that even severe food allergy patients can have an acute abdominal condition from the more common non-allergic causes. All patients with acute abdominal symptoms must be studied carefully, and in some cases surgery may have to be done to be on the safe side.

4065 East Cooper Street

News Items

SYMPOSIUM ON ALLERGY

Wayne University College of Medicine and the Allergy Clinic of Detroit Receiving Hospital held a Symposium on Modern Concepts of Allergic Diseases at the Auditorium, College of Medicine, Wayne University, Detroit, on November 29. Jack Rom, M.D., F.A.C.A., Instructor in Clinical Medicine, acted as chairman. The following program was presented:

Immunologic Aspects of Allergic Disease—recent progress and present status
DR. SIDNEY FRIEDLAENDER, F.A.C.A., Instructor in Clinical Medicine
Pharmacologic Aspects of Allergic Diseases
DR. VICTOR A. DRILL, Professor of Pharmacology
Pathology of Allergic Disease
DR. OSBORNE A. BRINES, Professor of Pathology
Internal Medicine and Allergy—recent progress, the collagen diseases
DR. SAMUEL JACOBSON, Assistant Professor of Clinical Medicine
Allergy and the Cardiovascular System
DR. JACK ROM, F.A.C.A., Instructor in Clinical Medicine
Gastrointestinal Allergy
DR. HOMER HOWES, Instructor in Clinical Medicine
Neurological Aspects of Allergy
DR. GABRIEL STEINER, Professor of Neuropathology
Psychiatric Aspects of Allergy
DR. JAMES C. MOLONEY, Associate Professor of Psychiatry
Allergic Dermatoses
DR. LOREN W. SHAFFER, Professor of Dermatology
Ocular Allergy
DR. ALBERT D. RUEDEMANN, Professor of Ophthalmology
The Management of Allergic Problems in the Surgical Patient
DR. ALEX S. FRIEDLAENDER, F.A.C.A., Instructor in Clinical Medicine

ASSOCIATION OF MILITARY SURGEONS

The 1950 Convention of The Association of Military Surgeons of the United States was held November 9-11 at the Hotel Statler in New York City. Appropriate to the times, the programs dealt with civil defense, the defense role of the physician, aviation medicine, rehabilitation, military medicine, surgery, sanitation, and discussions on the use of the newest therapeutic and prophylactic agents in emergency conditions. Norvin C. Kiefer, M.D., F.A.C.A., of Bethesda, Maryland, spoke on Civil Defense Planning.

OHIO VALLEY SOCIETY

At the Ohio Valley Allergy Society meeting, held at the Seneca Hotel on October 7 and 8, new officers were elected. C. B. Bohner, M.D., F.A.C.A., Indianapolis, Indiana, was elected president; S. William Simon, M.D., F.A.C.A., Dayton, Ohio, is president-elect; and D. J. Parsons, M.D., F.A.C.A., Springfield, Ohio, was re-elected secretary-treasurer. Members of the College who presented papers are Dr. William Mount, Crawfordsville, Indiana, and Dr. John Martin of Columbus, Ohio.

COURSE ON ALLERGIC DISEASES

The New School for Social Research, 66 West 12th Street, New York City, announces a course of four lectures by Arthur F. Coca, M.D., F.A.C.A., covering the causes, the diagnosis, and the prevention of allergic diseases. New methods of

diagnosis and treatment will be discussed and illustrated. A demonstration of the pulse-dietary technique will be extended to all those attending the course. Dates of the lectures are January 23, 24, 30, and 31, 1951, at 8:30 P.M.

BRAZILIAN INSTITUTE FOR THE HISTORY OF MEDICINE

At a meeting of the Brazilian Institute for the History of Medicine at the General Polyclinic of Rio de Janeiro on July 19, two members of the Bahian Institute of the History of Medicine presented historical papers: Professor Alberto Silva and Professor Jose Lima. Dr. Involino de Vasconcellos presided at the meeting. Volume I, Number 2, of the official organ of the society, *Brazilian Review of the History of Medicine*, is circulating. Members were reminded of the First Brazilian Congress on the History of Medicine to be held in July of 1951.

The birthday of Oswaldo Cruz was celebrated by the institute on August 4 with an oration on yellow fever by Dr. Carlos da Silva Araujo.

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

The ninth annual meeting of the American Academy of Dermatology and Syphilology was held in Chicago, December 2 through December 7, 1950. Special courses in histopathology and mycology were presented, December 2 and 3, at the Medical Schools of the University of Illinois and Northwestern University. Special courses in x-ray and radium therapy, bacteriology of the skin, anatomy and embryology of the skin, and special problems in dermatohistopathology were held at the Palmer House. Extensive scientific and technical exhibits were set up in connection with the meeting.

RED CROSS NATIONAL BLOOD PROGRAM

Dr. Russell Landram Haden, medical educator, author, and recently head of the Department of Medicine at the Cleveland (Ohio) Clinic, has been appointed medical director of the Red Cross National Blood Program, Gen. George C. Marshall, the organization's president, has announced. Doctor Haden will direct the medical aspects of the blood program as it is expanded to provide blood, plasma, and other derivatives for the nation's hospitals and for military and civil defense needs.

ALLERGIST WANTED

The director of a large hospital serving a community of over 200,000 people, is seeking a full-time allergist. Further information may be obtained from The American College of Allergists, 423 La Salle Medical Bldg., Minneapolis 2, Minn.

Since the appearance of Dr. Ira R. Morrison's article entitled "An Instrument Devised to Produce Painless Scratches" in the last issue of the ANNALS, many requests have been received for information as to where the instrument may be purchased. Doctor Morrison informs us, in reply to our inquiry, that the commercial name for the device is Micrometer Scratcher. The instruments are now being made by hand in a local machine shop. At present, the price is $22.50. The response he has received since publication of the article, however, has led him to believe that it will be necessary to produce them on a production basis in the near future. At present, the instruments may be ordered directly through Doctor Morrison, Suite 11, Blair Bldg., Atchison, Kansas.

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